# PSYCHOSOCIAL AND PSYCHOPHYSIOLOGICAL CHARACTERISTICS OF ATRIAL FIBRILLATION PATIENTS AND THEIR INFLUENCE ON THE PROTHROMBOTIC STATE AND PROGNOSIS

**By**

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**A thesis submitted to the University of Birmingham for the degree of Doctor of Philosophy in the Faculty of Science**

**August 2006**

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## ABSTRACT

*The prevalence and prognostic significance of depression and anxiety in patients with atrial fibrillation*

**Objective:** The purpose of the current study was to examine the persistence of depression and anxiety in atrial fibrillation (AF) patients, and their implications for future quality of life (QoL) and major adverse cardiovascular events (MACE).

**Methods:** The Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), and Dartmouth Care Cooperative Information Project (COOP) charts were complete by 101 patients with AF and 97 patients with hypertension. Six-month survival status and presentation for MACE were ascertained; QoL was re-assessed at six-months using the Dartmouth COOP charts.

**Results:** Symptoms of depression prevailed in 38% of patients with AF, with elevated state and trait anxiety being reported in 28% and 38% of patients, respectively. No significant differences in depression, state anxiety, and QoL were observed between patients with AF and hypertension, although AF patients displayed higher levels of trait anxiety. Analysis of survival status and MACE was not conducted due to an insufficient number of events. Symptoms of depression and anxiety at baseline, female gender, ethnicity, and employment status were significantly correlated with QoL at six-months in patients with AF. In a multiple regression model in which all of these variables were entered, baseline depression scores provided the best independent prediction of six-month QoL, although gender and employment status also entered the model.

**Conclusions:** The prevalence of depression and anxiety in patients with AF is comparable to patients following a myocardial infarction. Baseline symptoms of depression were the strongest independent predictor of QoL at six-months in patients with AF.

## ABSTRACT

*Effects of acute mental and postural stress on haemorheology, endothelial, and platelet reactivity in patients with atrial fibrillation*

**Background:** The purpose of the study was to examine the effects of acute mental stress, acute postural stress, and hydration status on haemorhelogy, endothelial function, and platelet reactivity in patients with atrial fibrillation (AF).

**Methods:** Fourteen male patients with AF (6 paroxysmal AF and 8 permanent AF), 10 patients with hypertension, and 10 healthy controls underwent four testing sessions; completing two mental stress tasks (mental arithmetic) and two postural stress tasks ($64^0$ head-up tilt). Cardiovascular and rheological reactivity, in addition to plasma von Willebrand Factor (vWF), E-selectin (sE-sel), P-selectin (sP-sel), intra-platelet levels of P-selectin (pP-sel) and measures of platelet morphology were obtained after 20 minute of supine rest, immediately following the stress task, and at 30 and 60 minutes recovery.

**Results:** Acute mental stress yielded a significant increase in all cardiovascular variables, haematocrit, and mean platelet volume (MPV). Postural stress evoked significant increases in haematocrit, sE-sel, platelet count, MPV, sP-sel, and a significant decrease in intra-platelet P-selectin. Hyperhydration caused a significant reduction in blood pressure in hypertensive patients, as well decreasing markers of endothelial perturbation and platelet morphology both at rest and in response to the stress tasks.

**Conclusions:** Anecdotal and epidemiological evidence has linked behavioural activities to the trigger of acute coronary syndromes (ACS). The current study adds some insight into the potential pathophysiological mechanisms through which acute mental stress and postural change may trigger the onset of ACS.

## DEDICATION

This thesis is dedicated to my family and friends.

Thank-you for your love, support, belief, motivation and inspiration.

**ACKNOWLEDGMENTS**

I would like to thank all the patients who contributed to the cause over the last three years – thank you for the valuable words of wisdom and funny anecdotes. I would like to thank Doug, Greg, and Deirdre for the excellent opportunity & supervision. A special thanks to all at the University Department of Medicine, particularly Anirban (cheers for being a reliable wing-man, motivator, recruiter, and genuinely nice guy), Rumi (thanks for the stories, support, words of wisdom – hope I haven't been too much of a jinx?!), Andrea and Jo (the constant counselling and pick-me-ups have been much appreciated), and Ruby (cheers for listening and always smiling).

Personally, I would like to congratulate Kev and Dolf for surviving three years of living with me, but also thank them for always having an open door. To my family, Mum, Dad, Kate, and saffy – thanks for the constant and infallible love and support. To my friends, in particularly James and Lesley, thank-you for being you – its true what they say 'it's the people you knew in the beginning who you'll need in the end'.

Finally, I would like to pay a special thanks to two people who have contributed immeasurably to the completion of this thesis. Deirdre, thank-you for putting up with me, supporting me, listening to me, but most importantly thanks for never letting me give in – think we made a good team. Mike, thank-you will never suffice. I love ya kidda. Best mates forever.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ACC | American College of Cardiology |
| ACCP | American College of Chest Physicians |
| ACE | Angiotensin-converting-enzyme |
| ACS | Acute coronary syndromes |
| ADP | Adenosine diphosphate |
| AF | Atrial fibrillation |
| AFFIRM | Atrial fibrillation Follow-up Investigators of Rhythm Management |
| AFI | Atrial Fibrillation Investigators |
| AHA | American Heart Association |
| aPTT | Activated partial thromboplastin time |
| AV | Atrioventricular |
| BDI | Beck Depression Inventory |
| BIA | Body impedance analysis |
| BP | Blood pressure |
| BPL | Bound plasma lysate |
| β-TG | Beta-thromboglobulin |
| CABG | Coronary artery bypass graft |
| CAD | Coronary artery disease |
| CHD | Coronary heart disease |
| CHF | Congestive heart failure |
| CRP | C-reactive protein |
| CTAD | Citrate theophylline adenosine dipyridamole |
| CVD | Cardiovascular disease |

| | |
|---|---|
| DBP | Diastolic blood pressure |
| DC | Direct current |
| ECG | Electrocardiogram |
| ECW | Extracellular water |
| EDTA | Ethylenediaminetetraacetic acid |
| ELISA | Enzyme-linked immunosorbant assay |
| ESC | European Society of Cardiology |
| FBC | Full blood count |
| FVII:C | Clotting factor VII |
| FVIII:C | Clotting factor VIII |
| FXII:C | Clotting factor XII |
| GPIbα | Glycoprotein Ibα |
| GPIIb/IIIα | Glycoprotein IIb/IIIα |
| Hb | Haemaglobin |
| Hct | Haematocrit |
| HDL | High density lipoprotein |
| HPA | Hypothalamic-pituitary-adrenocortical |
| HR | Hazard ratio |
| ICW | Intracellular water |
| IL-6 | Interleuken-6 |
| IQR | Inter quartile range |
| LV | Left ventricular |
| LVEF | Left ventricular ejection fraction |
| MACE | Major adverse cardiovascular events |
| MAP | Mean arterial pressure |

| | |
|---|---|
| MI | Myocardial infarction |
| mL | Millilitres |
| MPM | Mean platelet mass |
| MPV | Mean platelet volume |
| $Na^+$ | Sodium |
| NASPE | North American Society of Pacing and Electrophysiology |
| NICE | National Institute of Clinical Excellence |
| NHS | National Health System |
| NVAF | Non-valvular atrial fibrillation |
| OR | Odds Ratio |
| PAA | Plasminogen activator activity |
| PAF | Paroxysmal atrial fibrillation |
| PAI-1 | Plasminogen activator inhibitor-1 |
| PBS | Phosphate buffered saline |
| PASAT | Paced auditory serial addition test |
| PIAF | Pharmacological Intervention in Atrial fibrillation |
| PiMS | Patient information Medical System |
| PPP | Platelet poor plasma |
| PR | Pulse rate |
| PRP | Platelet rich plasma |
| PTCA | Percutaneous transluminal coronary angiography |
| PTT | Prothrombin time |
| PV | Pulmonary vein |
| PVD | Peripheral vascular disease |

| | |
|---|---|
| QoL | Quality of Life |
| RACE | Rate Control Versus Electrical Cardioversion |
| RBC | Red blood cell |
| RR | Relative Risk |
| SA | Sinoatrial |
| SAM | Sympathetic-adrenal-medullary |
| SEM | Standard error of the mean |
| SBP | Systolic blood pressure |
| SD | Standard deviation |
| SF-36 | Short-Form-36 |
| SPAF | Stroke prevention in atrial fibrillation |
| SPL | Supernatant platelet lysate |
| sE-Sel | Soluble E-selectin |
| sP-Sel | Soluble P-selectin |
| SSRIs | Selective serotonin reuptake inhibitors |
| STAF | Strategies of Treatment for Atrial fibrillation |
| STAI | State-Trait Anxiety Inventory |
| TAT | Thrombin-antithrombin |
| TBW | Total body water |
| TIA | Transient ischaemic attack |
| TNF-α | Tumour necrosis factor-α |
| TOE | Transoesophageal echocardiography |
| t-PA | Tissue-type plasminogen activator |
| UK | United Kingdom |
| USA | United States of America |

| | |
|---|---|
| vWF | von Willebrand |
| WBC | White blood cell |
| WGA-ESC | Working Group on Arrhythmias of the European Society of Cardiology |
| WHO | World Health Organisation |

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# CHAPTER 1

# Introduction

## 1.1 General Introduction

### 1.1.1 Atrial Fibrillation

Atrial fibrillation (AF) is the most commonly encountered cardiac arrhythmia in clinical practice, and is defined as a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation [1]. AF can be observed on an electrocardiogram (ECG) by the absence of a P-wave, which is replaced with rapid oscillations or fibrillatory waves. These fibrillatory waves can vary in size, shape and timing, and are generally associated with an irregular ventricular response when the atrioventricular (AV) node is intact [2]. The ventricular response in AF is dependent on three major factors; AV nodal properties, the levels of sympathetic and parasympathetic tone acting on the sinoatrial (SA) node, and the effect that anti-arrhythmic drugs (i.e. beta-blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides) have on AV nodal conduction [3]. The exact aetiology of AF is complex, but is thought to involve several coexisting re-entrant wavefronts continuously sweeping around the atria in an irregular motion, repeatedly encountering excitable myocardium [4].

### 1.1.2 Epidemiology

Current estimates suggest that AF afflicts approximately 2.2 million Americans [5]. In the United Kingdom (UK) approximately 740,000 individuals are thought to have AF [6], with more than 46,000 new cases being diagnosed each year [7]. The majority of epidemiological studies have been population-based, predominantly looking at the prevalence of AF in Western countries, comprised mainly of Caucasians. The Cardiovascular Health and Framingham studies reported prevalence figures between 2.3

and 6.2% in individuals aged over 30 years [8,9]. In the Renfrew-Paisley cohort, the prevalence of AF was 8 per 1000 in males and 4.2 per 1000 in females [10], increasing to 19.2 persons per 1000 when the study population excluded those aged <65 years [11]. The prevalence of AF has been shown to increase with advancing age. The Framingham Study demonstrated an increase in prevalence from 0.5% in people aged 50-59 years to almost 9% in people aged 80 years or older [9], a trend borne out in other studies [8,10,12]. The prevalence of AF in non-Caucasian populations has received relatively little attention. The Cardiovascular Health Study demonstrated that there was a lower incidence of AF in Afro-Caribbeans compared to a Caucasians [8]. The Northern Manhattan Stroke Study observed that of patients presenting an ischaemic stroke, AF was more common in Caucasians (29%) than in either Black (11%) or Hispanic (11%) patients [13]. Further, a general practice survey in West Birmingham, UK, examining the prevalence of AF in an South-Asian population aged >50 years, found that although this ethnic group comprised 65% of the population, the prevalence of AF was only 0.6% [14].

Population-based data from the Framingham Study demonstrates that the prevalence of AF in persons aged 65-84 years has substantially increased over a 21 year period. Between 1968 and 1989, the prevalence rose from 3.2% to 9.1% in men, with a smaller and but non-significant increase observed for females [9]. Explanations for the increasing prevalence include the aging population, greater awareness and surveillance by diagnosing doctors, and an increased myocardial infarction (MI) survival rate [4].

### 1.1.3 Cost of atrial fibrillation

The increased prevalence of AF is accompanied with an increased economic burden to our national health service (NHS). Stewart and colleagues (2004) calculated the economic cost of AF to the health and social services in the UK in 1995, and based on epidemiological trends, projected this estimate to 2000. The authors estimated that in 2000 the 'direct' cost of health care for AF patients would be £459 million or 0.97% of the total NHS expenditure [15]. Analogous figures are not available for the United States; however, a recent editorial stated that similar economic costs are probably incurred [16], as the cost of acute hospital admissions and total Medicare payments were significantly higher in patients with AF [17].

### 1.1.4 Classification of atrial fibrillation

AF is an arrhythmia that has a heterogeneous clinical presentation. Although several classification schemes have been proposed, none have fully accounted for all aspects of AF [18-21]. In 2003, the Working Group on Arrhythmias of the European Society of Cardiology (WGA-ESC) and the North American Society of Pacing and Electrophysiology (NASPE) recognised the need for consensus on the terminology and classification of AF [22]. Table 1.1 shows the WGA-ESC and NASPE clinical classifications of AF. This proposed scheme has been adopted by the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) [23] and the National Institute of Clinical Excellence (NICE) guidelines for the management of AF in the UK [24].

Table 1.1: Classification of atrial fibrillation

| Terminology | Clinical Features | Pattern |
|---|---|---|
| Initial event<br>(first detected episode) | Symptomatic<br>Asymptomatic (1st detected)<br>Onset unknown (1st detected) | May or may not occur |
| Paroxysmal AF | Spontaneous termination <7 days and most often <48 hours | Recurrent |
| Persistent AF | Not self-terminating<br>Lasting >7 days | Recurrent |
| Permanent AF | Not terminated<br>Terminated but relapsed<br>Cardioversion not attemptedt | Established |

### 1.1.5 Risk factors

Numerous risk factors have been identified for the development of AF and these can be broadly grouped into cardiovascular and non-cardiovascular (Table 1.2). In some individuals with AF, no predisposing factor can be identified and patients are subsequently classified as "lone AF". The true prevalence of lone AF varies and is highly dependent upon the definition and population studied. Kopecky and colleagues demonstrated that over a 30-year follow-up period 97 patients (2.7%) developed lone AF (atrial fibrillation in the absence of overt cardiovascular disease or precipitating illness) [25]. Other studies examining the presence of lone AF are confounded by the inclusion of hypertensive and diabetic patients [26].

Cardiovascular risk factors are commonly associated with the development of AF. Hypertension and/or hypertensive heart disease is the most common underlying disorder in patients who have AF, accounting for approximately 50% of cases [11,27-29]. In addition to advancing age, the Framingham study demonstrated that the development of AF was significantly associated with diabetes (OR, 1.4 for men and 1.6 for women), hypertension (OR, 1.5 for men and 1.4 for women), congestive heart failure (OR, 4.5 for men and 5.9 for women), and valve disease (OR, 1.8 for men and 3.4 for women)

[9]. Psaty and colleagues also demonstrated that age, and coronary and valvular disease were important risk factors for the development of AF [11]. However, the authors demonstrated that levels of blood pressure and glucose were more important predictors than the diagnoses of high blood pressure and diabetes *per se* [11]. Ischaemic heart disease is probably the most common underlying cause of AF in the UK [30]. In the Framingham study, MI was significantly associated with the development of AF in men. Krahn and colleagues also demonstrated that the risk of AF was associated with MI (relative risk (RR) 3.62), angina (RR 2.84), and S-T wave abnormalities in the absence of ischaemic heart disease (RR 2.21) [31].

AF is the most common arrhythmia reported following cardiac surgery. Among patients undergoing coronary artery bypass grafting (CABG), 33% developed AF in the post-operative period [31]. Independent predictors of post-operative AF include increasing age, male sex, hypertension, need for an intra-operative balloon pump, post operative pneumonia, ventilation for >24 hours, and return to the intensive care unit [31].

Hyperthyroidism is the most prominent non-cardiovascular variable associated with the development of AF [32], with AF occurring in 9-22% of patients with thyrotoxicosis [33]. Signs of hyperthyroidism may be less obvious in the elderly, and indeed sub-clinical hyperthyroidism (indicated by a low TSH, and normal or high T4 in an asymptomatic patient) has been reported in patients with AF [34].

Table 1.2: Causes of atrial fibrillation

| **Cardiovascular causes** | |
|---|---|
| *Common* | *Less common* |
| ➢ Ischaemic heart disease<br>➢ Hypertension<br>➢ Rheumatic heart disease<br>➢ Heart failure<br>➢ Sick sinus syndrome<br>➢ Pre-excitation syndromes (i.e. Wolf-Parkinson-White<br>➢ Cardiac surgery | ➢ Cardiomyopathy or heart muscle disease<br>➢ Pericardial disease, including effusion and constrictive pericarditis<br>➢ Sinus node dysfunction<br>➢ Atrial septal defect<br>➢ Atrial myxoma |

| **Non-cardiovascular causes** | | |
|---|---|---|
| *Metabolic causes* | *Respiratory* | *Other causes* |
| ➢ Thyrotoxicosis<br>➢ Low potassium, magnesium, or calcium<br>➢ Drugs<br>➢ Alcohol<br>➢ Postoperative (non-cardiac surgery)<br>➢ Hypothermia | ➢ Pneumonia<br>➢ Carcinoma<br>➢ Pulmonary thromboemolism<br>➢ Trauma<br>➢ Thoracic | ➢ Vagal AF<br>➢ Adrenergic AF |

### 1.1.6 Prognosis

#### 1.1.6.1 Morbidity and mortality

The majority of the morbidity associated with AF is the result of haemodynamic changes, and thromboembolic complications [24]. From the outset, AF patients are haemodynamically compromised. The absence of atrial systole, combined with the rapid irregularity of the ventricular response causes a reduction in cardiac output of between 10-20% [36]. This disturbance is more important in the elderly and/or those with progressive impairment of left ventricular contraction, in whom atrial systole contributes increasingly (>30%) towards the overall stroke volume. It has also been speculated that sudden increases in ventricular rate associated with uncontrolled AF may lead to the development of critical cardiac ischaemia or even MI in patients with significant coronary artery disease (CAD) [37]. The main haemodynamic symptoms reported during AF are palpitations, dyspnoea, dizziness, and angina. Syncope is rare in people with AF, unless associated with sick sinus syndrome or pre-excitation syndromes, such as Wolf-Parkinson-White syndrome. As expected, these symptoms are

more pronounced during physical activity, with a rapid ventricular response substantially impairing exercise tolerance [30].

AF is associated with the development of a prothrombotic state [37], with patients at an increased risk of thromboembolic complications, such as stroke [38]. The development of ischaemic stokes in AF results predominately from cardioemboli, most commonly occurring in the left atrial appendage. Manning and colleagues demonstrated left atrial thrombi in more than 40% of patients with acute thromboembolism and newly diagnosed AF [40]. The fulfilment of Virchow's Triad for thrombogensis [41], through abnormalities of flow (i.e. stasis of blood within the left atrium), abnormalities of the vessel wall (i.e. endothelial/endocardial damage), and abnormalities in blood constituents (i.e. platelet hyper-reactivity, coagulation-fibrinolytic imbalance) leads to the development of a hypercoagulable or prothrombotic state, and is likely to be of significance in intra-atrial thrombogenesis.

Data from the Framingham study revealed that non-valvular AF (NVAF) is an independent risk factor for stroke, accounting for approximately 10-15% of all ischaemic strokes, and nearly a quarter of strokes for those >80 years. Among those patients with NVAF, the stroke rate is approximately five times higher than for individuals in sinus rhythm [38]. AF patients also have a worse outcome following a stroke, with an elevated 30-day [42-43] and 12-month mortality [42], and stroke recurrence rates [42]. The severity of stroke is also greater in patients with AF [43-44], which is coupled with longer hospital stays [44] and lower discharge rates to their own homes [44].

AF is associated with an increased risk of mortality. Data from the Framingham study demonstrated that following adjustment for age, hypertension, smoking, diabetes, left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack, AF was associated with an odd ratio (OR) for death of 1.5 (95% CI, 1.2 to 1.8) in men and 1.9 (95% CI, 1.5 to 2.2) in women [26].

#### 1.1.6.2 Psychological prognosis

In addition to established cardiovascular risk factors such as diabetes, hypertension, and smoking, psychological variables have been implicated in the aetiology and progression of coronary heart disease (CHD). Numerous studies have examined the prognostic significance of depression and anxiety in patients with CHD, although there are no published data on whether such psychological variables can predict future cardiovascular morbidity and mortality (cardiac and all-cause) in patients with AF. Accordingly, the literature examining the impact of depression and anxiety on prognosis in patients with CHD will be reviewed.

##### 1.1.6.2.1 Depression

Table 1.3 summarises the main studies examining the impact of depression on future cardiovascular morbidity and mortality (cardiac and all-cause) in patients with CHD [45-75]. Eight studies examined the impact of depression on all-cause mortality [45,53,61,63-64,70,72,75], with positive and negative outcomes findings being reported in equal measure. Kauffman and colleagues [61] demonstrated that although depression failed to predict all-cause mortality over six-month follow-up (OR 2.46; CI, 0.86-6.98), a positive association was observed at 12-months (OR 2.34; CI, 1.18-4.65). Carney and

colleagues were the only group to correct for known cardiac risk factors (age, smoking, LVEF, diabetes), demonstrating that even following statistical adjustment their positive association between depressive disorder and 30-month all-cause mortality persisted (HR [adj] 2.4; CI, 1.20-4.70) [72].

The majority of research examining the prognostic significance of depression has centred on its impact on cardiovascular mortality. Twenty publications reporting on 13 studies have examined this relationship [46-52,54-60,62,65-69], mainly in patients following a MI [46-52,58-60,62,65,67-68]. Frasure-smith and colleagues [49-52] were one of the 10 [47-52,54-62,65-66] positive studies to emerge, demonstrating that depressive symptoms were predictive of cardiovascular mortality in the initial six months following a MI (OR 6.24; CI, 1.88-20.67) even after adjustment for known cardiac risk factors (HR [adj] 4.29; CI, 3.14-5.86). Although Schleifer and colleagues demonstrated that depression was not predictive of cardiovascular mortality over a three month follow-up period (OR 0.59; CI, 0.20-1.74) [46], other investigators have replicated the results of Frasure-Smith and colleagues in follow-up periods up to 10 years [54-62,65-66].

Lane and colleagues [67-68] were one of only three groups [46,67-68,69] to report no impact of depression on cardiovascular mortality following MI, demonstrating that depressive symptoms failed to predict cardiovascular mortality at 12-month (OR 1.15; CI, 0.49-2.70) [67] and 3-years (OR 0.84; CI, 0.37-1.91) [68]. With the authors reporting similar rates of mild to moderate depressive symptoms, socio-economic status, and 12-month post-discharge mortality rates to Frasure-Smith and colleagues [49-52], the authors speculated about potential reasons for the discrepancies in findings.

Lane et al. suggested that some of the inconsistency may have arisen from the exclusion of patients who died prior to discharge from hospital. However, further analysis by the authors revealed that even when they excluded such patients in their analyses, symptoms of depression still failed to predict mortality [67].

As many of the questionnaires (e.g. Beck Depression Inventory) assessing depressive symptoms have a significant somatic component, a more robust explanation of the discrepancy in outcome may be centred around the confounding issue of disease severity. Many studies reporting an association between depression and mortality have also reported a positive association between cardiac disease severity and depressive symptomatology. In contrast however, Lane and colleagues [68] failed to find any association between depression and medication status at discharge, nor, with exception of diabetes, any conventional cardiac risk factors (e.g. blood pressure status, smoking hyperlipidaemia), which they suggested may account for their null findings. Further support for this hypothesis has arisen from studies [47-48,61-62] where the significant association between depression and mortality following an MI has been abolished when disease severity has been statistical adjustment for.

Two recent meta-analyses have examined the relationship between depressive symptoms and depressive disorders on cardiac and all-cause mortality in patients with CHD. The first by Barth and colleagues [76], including patients following an initial CHD event (MI, coronary artery bypass graft [CABG], percutaneous transluminal coronary angiography [PTCA]) or angiographically validated CHD, examined the association between depressive symptoms and disorders on cardiac and all-cause mortality. The review, including 29 publications reporting on 20 studies, demonstrated

that in both short and medium term (OR 2.24; CI, 1.37-3.60), and long term (≥5 years) follow-up (OR 1.78; CI, 1.12-2.83) studies, depressed CHD patients were at an increased risk of all-cause mortality. The authors found that even after adjustment for know cardiac risk factors (age, sex, physical illness, smoking, hyperlipidaemia, hypertension) patients exhibiting depressive symptoms were still at an increased risk of dying from any cause in the first two years after their initial assessment (HR [adj], 1.76; CI, 1.27-2.43). Further analysis also revealed that depressive symptoms were a slightly better predictor for cardiac mortality (HR [adj], 2.07; CI, 1.31-3.27) than for all-cause mortality (HR [adj], 1.76; CI, 1.27-2.43).

Six of the 20 included studies examined the impact of depressive disorders. Although no impact on mortality was observed within the first 6 months (OR, 2.07; CI, 0.82-5.26), the risk of depressive disorders was more than two times greater for CHD patients with clinical depression (OR, 2.61; CI, 1.53-4.47) in the two years after their initial assessment. The limited number of studies reporting adjusted risk analysis, revealed an adjusted HR for all-cause mortality of 4.29 (CI, 3.14-5.86). However, Carney and colleagues were the only group to report follow-up over two years, demonstrating an adjusted HR of 2.4 (CI, 1.20-4.70) [72].

The second meta-analysis by van Melle and colleagues [77], examined the impact of depression post-MI (≤3 months) on cardiac and all-cause mortality and cardiovascular events. The authors included 22 studies, 15 of which were also included in the meta-analysis by Barth and colleagues. This review demonstrated that depression post-MI was significantly associated with a two-fold increased risk of all-cause mortality (OR, 2.38; CI, 1.76-3.22), cardiac mortality (OR, 2.59; CI, 1.77-3.77), and cardiovascular

events (OR 1.95; 1.33-2.85). Secondary analysis revealed that the significant association between post-MI depression and all-cause and cardiac mortality was not influenced by the way that depression was assessed (questionnaire vs. psychiatric interview). Although non significant (p=0.08), the authors revealed that there was a trend for the year of data collection (pre 1992) to influence the effect of depression on mortality, with stronger associations found in earlier studies (OR 3.22; CI, 2.14-4.86) compared with the later studies (OR 2.01; CI, 1.45-2.78).

1.1.6.2.2 Anxiety

In contrast to the plethora of research examining the impact of depression, only eight studies have examined whether symptoms of anxiety can predict outcome in patients with CHD (see Table 1.4) [63-64,67,74,78-81]. Pfiffner and colleagues [81] were one of the four studies [63-64,67,81] examining whether symptoms of anxiety can predict all-cause mortality in CHD patients. In contrast to the other three studies, the authors demonstrated a significant association between symptoms of anxiety and death from any cause over a seven years follow-up period (OR 1.19; CI, not reported). Caution is warranted when interpreting such findings as the authors limited the analysis to male patients less than 60 years and failed to adjust statistically for know cardiac risk factors.

Four studies examined whether anxiety can predict cardiovascular mortality over follow-up periods ranging from one to 12 years [67,78-79,81]. The two studies with a protracted follow-up period (8 and 12 years) demonstrated a positive association between symptoms of anxiety and death from cardiac causes [78-79]. Frasure-Smith and colleagues [80] were the only group to undertake and report statistical adjustment, demonstrating that when various baseline and treatment variables were accounted for,

the positive association (OR 1.21; CI, 1.01-1.46) between anxiety and cardiac mortality was abolished (HR [adj] 1.14; CI, 0.93-1.38).

Two studies have examined the effect of anxiety on future cardiovascular events. Denollet and colleagues [79] demonstrated that in patients (left ventricular ejection fraction (LVEF) $\leq$50%) following an MI, anxiety was predictive of future cardiovascular events (e.g. recurrent MI, CABG, PTCA) (OR 3.4; CI, 1.2-9.6). Strik and colleagues [74] replicated such findings over a shorter follow-up period (3.4 years). The authors demonstrated that even after adjustment for certain risk factors (e.g. age, LVEF, and use of anti-depressants) the impact of anxiety on future cardiovascular events persisted (HR [adj] 3.01; CI, 1.20-7.60).

1.1.6.2.3 Possible mechanisms linking negative emotions to cardiovascular outcomes

Despite the evidence that negative emotions (particularly depression) increase the risk of cardiovascular morbidity and mortality, no commonly accepted theory on the underlying mechanisms exists. Although research on the related mechanisms is sparse, current debate centres on "indirect" and "direct" theories. The "indirect" theory states that psychosocial factors may affect health related behaviours (eg, physical inactivity, poor diet, pharmacological non-compliance, smoking) which may in turn influence the risk of CHD [82]. The "direct" theory hypothesises that psychophysiological factors may directly lead to the development/progression of acute coronary syndromes (ACS). Currently the main candidate mechanisms linking negative emotions to cardiovascular outcome are (1) anti-depressant cardio-toxicity; (2) modification of health related behaviours; (3) alterations in the autonomic function; (4) haemostatic abnormalities; and (5) immunological dysregulation.

1.1.6.2.3.1 Anti-depressant cardio-toxicity

It is commonly recognised that certain anti-depressants, such as tricyclics and monoamine oxidase inhibitors, have cardio-toxic side effects. Such findings have prompted speculation over whether the excess in cardiac morbidity and mortality may be due to the effects of pharmacological therapy and not depression *per se* [83]. Although plausible, the available evidence suggests that antidepressants are unlikely to contribute significantly to the morbidity and mortality in depressed CHD patients. First, associations between depression and cardiovascular outcome were observed prior to the development of anti-depressant medication. Secondly, only a small proportion of anti-depressants have severe cardiotoxic side effects, and third, selective serotonin reuptake inhibitors (SSRIs) have few cardiotoxic side effects, and they currently are the frontline antidepressants for cardiac patients [84].

1.1.6.2.3.2 Modification of health related behaviour

The "indirect theory" speculates that a modification of health related behaviours following a MI may increase an individual's cardiovascular risk. A recent study by Ziegelstien and colleagues revealed that post-MI patients demonstrating mild to moderate levels of depression reported lower levels of adherence to low-fat diets, regular exercise and stress reduction programs, and are less likely to socialise [85]. A meta-analysis by Dimatteo and colleagues examined the effect of depression and anxiety on patient adherence to medical therapy [86]. The review, including 12 articles on depression and 13 on anxiety, revealed a substantial and significant relationship between depression and non-compliance (OR 3.03; CI, 1.96-4.89). However, the authors failed to find a significant association between anxiety and non-compliance.

Although plausible, evidence suggests that health related behaviours do not contribute significantly to the excess in morbidity and mortality in depressed CHD patients. First, in studies were depression has been shown to predict cardiovascular events (morbidity and mortality), no significant relationship has been shown between depression and cardiac risk factors (e.g. smoking status, social status) [49-52]. Secondly, in studies where depression has been shown to have prognostic significance, the statistical adjustment for cardiac risk factors (smoking, social support, physical activity) has failed to abolish the significant association [47-48,58-60,65,71].

1.1.6.2.3.3 Alterations in autonomic function

Neurohormonal dysregulation has emerged as the most plausible explanation for the effects of depression and anxiety on cardiac morbidity and mortality. An activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic-adrenal-medullary (SAM) system has been linked to an elevation of serum levels of cortisol and catecholamines. If such negative emotions and elevated hormone levels persist over time, free fatty acid levels, blood pressure, and total peripheral resistance will increase, altering the individuals cardiovascular risk profile [87]. In addition, autonomic dysregulation may predispose CHD patients to myocardial ischaemia, ventricular tachycardia, ventricular fibrillation, and sudden cardiac death [88].

1.1.6.2.3.4 Haemostatic abnormalities and immunological dysregulation

Abnormalities in the autonomic nervous system may also promote procoagulant and proinflammatory processes which have been implicated in the aetiology of ACS Musselman and colleagues demonstrated that healthy depressed individuals exhibited a 41% increased platelet aggregation in comparison to healthy non-depressed individuals

[89]. Although limited evidence is available for depressed CHD patients, Lagrissi-Thode and colleagues [90] found higher plasma concentrations of platelet factor-4 and β-thromboglobulin (two proteins that are secreted from alpha granules) for depressed patients with CHD compared to non-depressed patients with CHD.

As coronary artery disease (CAD) is now commonly regarded as a chronic inflammatory process it would appear reasonable to hypothesis that depression may lead to immunological dysregulation. Depression has been shown to enhance the production of proinflammatory cytokine, including Interleuken (IL)-6, C-reactive protein (CRP), and tumour necrosis factor-α (TNF-α) in medically healthy adults [91-92]. However, interpretation of such findings is made difficult by the failure to account for the confounding of medication and smoking status, acute infections present at time of assessment, and hospitalisation [93]. As with alterations in platelet reactivity, little attention has been paid to the link between depression and inflammation in patients with existing CHD. A study by Appels and colleagues, addressing this issue, revealed elevated levels of IL-1β and TNF-α in the coronary circulation in patients undergoing angioplasty due to severe angina [94].

### 1.1.7 Management

#### 1.1.7.1 Risk stratification for anti-thrombotic therapy

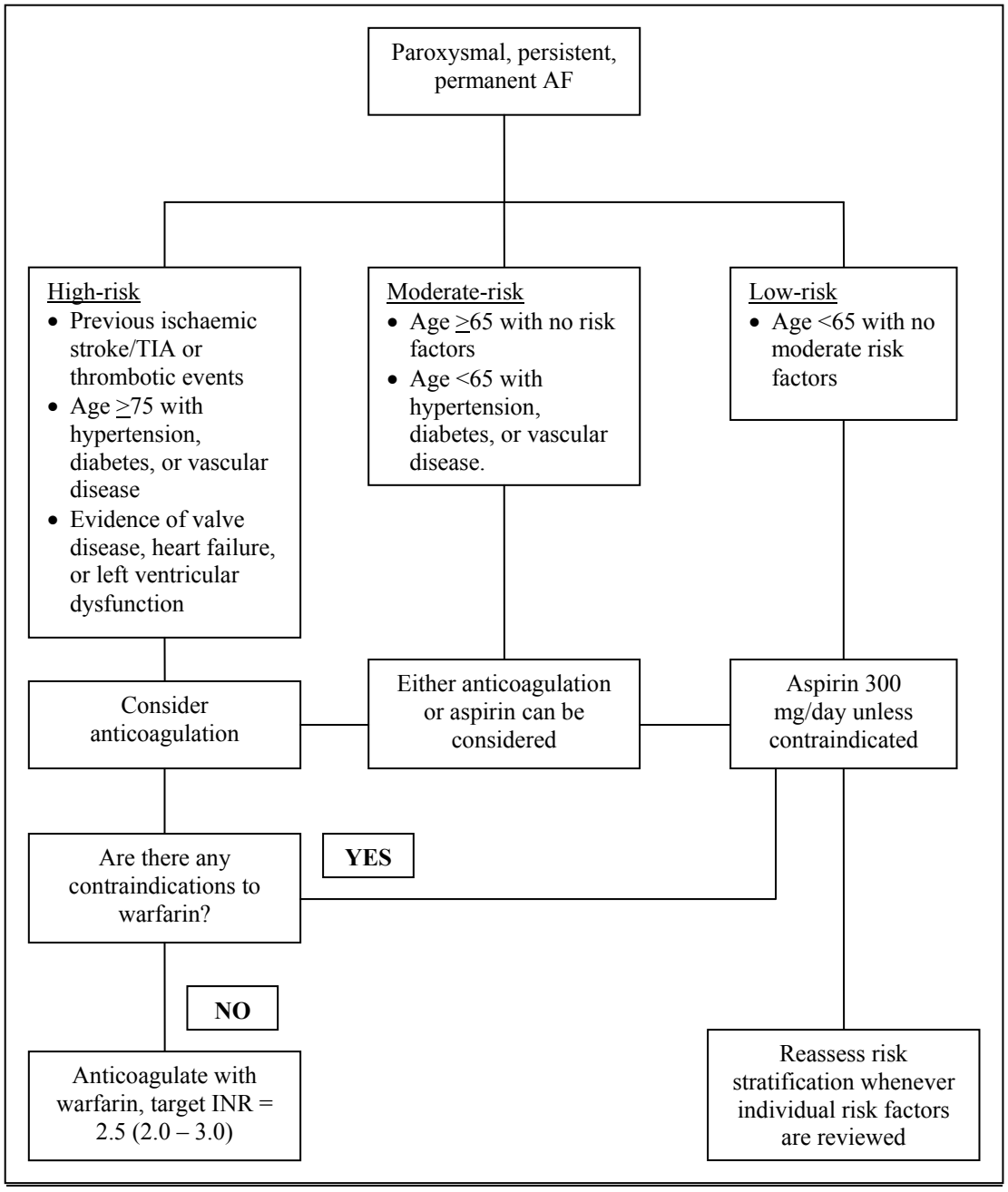
Numerous studies have investigated the degree to which anti-thrombotic regimes can decrease the risk of ischaemic stroke in AF. A recent meta-analysis of 13 studies (14,435 participants) demonstrated that dose-adjusted warfarin decreased the risk of ischaemic stroke by 33% compared to placebo, in combination with a 69% risk reduction in all cause mortality [95]. An earlier meta-analysis demonstrated that aspirin

therapy also has the potential to reduce the risk of stroke by 22% in comparison to placebo [96]. A comparative analysis of dose-adjusted warfarin and aspirin demonstrates the superiority of warfarin in reducing total stroke (RR 0.35, 95% CI 0.14 to 0.51) [96] and ischaemic stroke and/or systemic embolism (RR 0.59, 95% CI 0.40 to 0.86) [95]. In light of such findings, it is imperative that physicians are given guidance on (1) which patients should be considered for anticoagulation, and (2) how to tailor anti-thrombotic regime for an individual, based on variables such as age, co-morbidities, and contraindications. Several risk stratification models have been proposed (see Table 1.3), and pooled analysis from these findings has led to the development of the current UK National Institute of Clinical Excellence (NICE) guidelines on risk stratification for antithrombotic therapy (see Figure 1.1). In brief, the guidelines suggest that AF patients at high risk for stroke should be considered for warafin therapy (unless contraindicated), moderate risk patients can be considered for either aspirin or warfarin, and low risk patients prescribed asprin only. It is imperative that physicians realise that the assessment and reassessment of risk is a continual process and patients should be re-stratified based on the development of additional risk factors.

#### 1.1.7.2 Current recommendations for non-invasive treatment

Table 1.4 depicts the current non-invasive management aims and recommendations for the treatment of paroxysmal AF (PAF), persistent AF, and permanent AF [24]. In addition to the therapeutic strategies outlined, highly symptomatic patients can also be considered for invasive procedures such as radiofrequency catheter ablation, external/internal pacing, and surgical procedures.

Figure 1.1: Risk Stratification for anti-thrombotic therapy in AF patients [24]




INR = International Normalised Ratio; TIA = Transient Ischaemic attack; ≥ = equal to or greater than; ≤ = equal to or less than

Table 1.3: Summary of the main stroke risk stratification schemes proposed for patients with AF [97]

| Risk Stratification scheme | Risk Strata<br>High | Intermediate | Low |
|---|---|---|---|
| AFI (1994) | High – intermediate risk: aged ≥65 years; history of hypertension, CAD, or diabetes | | Aged <65 years; no high/intermediate risk features |
| SPAF (1995) | Women aged >75; SBP >160 mmHg; LV dysfunction | History of hypertension; no high risk features | No history of hypertension; no high risk features |
| Lip (1999) | All patients with previous TIA or cerebrovascular accident; aged ≥75 with diabetes or hypertension; clinical evidence of valve disease, heart failure, thyroid disease, and impaired LV function | Aged ≥65 with clinical risk factors: hypertension, diabetes, peripheral vascular disease, ischaemic heart disease; all patients ≥65 not in high risk | Aged <65 with no history of embolism, hypertension, diabetes, or other clinical risk factors |
| ACC/AHA/ESC (2001) | Aged ≥60 years with diabetes or CAD; aged ≥75 years (especially women); any age with risk factors (clinical heart failure, LVEF ≤35%; thyrotoxicosis, or hypertension); rheumatic heart disease, prosthetic heart valves; previous thromboembolism; persistent atrial thrombus on TOE | Aged <60 years with CAD but no risk factors; aged ≥60 years and risk factors | Aged <60 years and no risk factors |
| $CHADS_2$ (2001 & 2004) | One point scored for each of the following: recent congestive heart failure, hyp, aged ≥75 years, diabetes. Two points scored if there is a history of stroke or TIA. Total score available is six. Scores 3 – 6 = high risk, 1 – 2 = moderate risk, 0 = low risk | | |
| Framingham (2003) | Weighted point scoring system—points are given for the following risk factors: ↑ age (maximum score ≤10); sex (female = 6, male = 0); hypertension (≤4); and diabetes (6). Total score (maximum 31 points) corresponds to a predicted 5 year stroke risk | | |
| ACCP (2004) | Prior stroke, TIA, or systemic embolic event; aged >75 years; moderately to severely impaired LV function with or without CHF; hypertension or diabetes | Aged 65–75 years with no other risk factors | Aged <65 years with no risk factors |

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AFI = Atrial Fibrillation Investigators; AHA = American Heart Association; CAD = coronary artery disease; CHF = congestive heart failure; ESC = European Society of Cardiology; ;LV = left ventricular; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; SPAF = stroke prevention in atrial fibrillation; TIA = transient ischaemic attack; TOE = transoesophageal echocardiography

Table 1.4: Non-invasive management strategies for the treatment of atrial fibrillation

| | Management Aims | Recommendations |
|---|---|---|
| Paroxysmal AF | 1. Suppress the paroxysmsof AF<br>2. Control of heart rate during paroxysms of AF if they occur<br>3. Prevent associated thromboembolic complications | 1. Cardioversion<br>▪ If paroxysms persist (>7days/usually >48hour) consider either electrical cardioversion or pharmacological cardioversion to return patient to SR<br>2. Anti-arrhythmic prophylaxis<br>▪ If future paroxysms are mild and infrequent it may be possible to avoid chronic anti-arrhythmic prophylaxis or adopt a 'pill-in-the-pocket' approach<br>▪ If future paroxysms are symptomatic and frequent chronic prophylaxis with pharmacological therapy should be implemented<br>▪ Beta-blockers or low-dose sotalol are usually considered as a first line drugs<br>▪ If symptomatic episodes persist or the patient has intolerable side effects, Class Ic (i.e. flecainide, propafenone) and III drugs (sotalol, amiodarone) should be considered<br>3. Rate control prophylaxis<br>▪ Beta-blocker therapy will assist in reducing heart rate during paroxysms of AF<br>4. Anti-thrombotic prophylaxis<br>▪ As the annual rate of ischaemic stroke is 3.2% patients should be risk stratified for anti-thrombotic therapy (see Figure 1.1) |
| Persistent AF | 1. Increase the likelihood of maintaining SR following an electrical or pharmacological cardioversion<br>2. Prevent associated thromboembolic complications | 1. Cardioversion<br>▪ If AF persists for >7 days electrical cardioversion should be considered<br>2. Anti-arrhythmic prophylaxis<br>▪ Long term anti-arrhythmic prophylaxis should be given to help maintain SR (see PAF)<br>3. Anti-thrombotic prophylaxis<br>▪ Thromboembolic events occur in between 1% and 7% of patients who do not receive anticoagulation prior to cardioversion. Therefore patients should maintain therapeutic anticoagulation with warfarin (INR 2.5; 2.0 – 3.0) for a period of three weeks prior to, and four weeks following a successful cardioversion |
| Permanent AF | 1. Control of heart rate<br>2. Prevent associated thromboembolic complications | 1. Rate control<br>▪ Ventricular rate should be controlled between 60 and 80 beats per minute at rest, and between 90 and 115 beats per minute during moderate exercise<br>▪ Beta-blockers or calcium-antagonists are usually considered as first line drugs<br>▪ Adequate rate control is not always achieved through monotherapy. Beta-blockers/digoxin combination is the preferred first choice to control heart rate during normal daily activities, with a calcium-antagonist/digoxin combination preferred if the patient partakes in regular exercise<br>2. Anti-thrombotic prophylaxis<br>▪ As the annual rate of ischaemic stroke is 3.3% patients should be risk stratified for anti-thrombotic therapy (see Figure 1.1) |

## 1.2 Quality of life in patients with atrial fibrillation

### 1.2.1 Background

Whereas the epidemiology, clinical consequences, and costs of AF have been subject to considerable study, less attention has been paid to patient-related issues, such as quality of life (QoL). The concept of QoL emerged in the late 1940s, when the World Health Organisation (WHO) extended the definition of health to encompass the presence of physical, mental, and social well-being [98]. Since the 1980s, QoL issues have become more important in health care practice and clinical research, with a search of the Cochrane Controlled Trials Register demonstrating an increase from 0.34% in 1980 to 3.6% in 1997 in the number of cardiovascular trials reporting QoL as an end point [99].

Assessment of QoL has been used for a variety of purposes in health-care settings: to screen for psychological morbidity; prioritise patients for various treatment regimes; determine the choice of treatment; monitor patients' progress; and as an outcome measure in research studies and clinical trials [99-101]. QoL is particularly relevant to the treatment of chronic conditions such as AF, a condition that is not immediately life threatening but is likely to cause a substantial impairment in QoL [102]. A previous review of QoL studies in AF patients revealed various methodological weaknesses including small sample sizes, non-validated questionnaires, and highly selective patient populations. However, since this review was undertaken a number of new interventions, including pulmonary vein (PV) isolation, implantable defibrillators, and the Maze operation, have become more common procedures for symptomatic AF patients, and the impact of such interventions on QoL has not been reviewed. In addition, a number of recent randomised controlled trials have examined the impact of rate versus rhythm control strategies on QoL [103-106]. With rapid medical advances

and subsequent reductions in mortality, variations in QoL may be the only reliable way of differentiating between treatment options.

### 1.2.2 Non-interventional observational studies examining quality of life in atrial fibrillation patients

Five observational studies [107-111] have examined QoL, using the Short Form (SF) - 36, in a 'general' AF population, comprising of patients with paroxysmal AF and chronic AF, in addition to elderly and newly diagnosed AF patients (see Table 1.7). Four of these studies [107,109-111], compared AF patients with a control group: other CHD patients [107], general population [111], and healthy controls [107,109-110]. Three of these studies [107,109-110] reported a poorer QoL in AF patients on some [109-110] or all of the SF-36 subscales [107]. One study [108] comparing the QoL of male and female AF patients, revealed that women reported significantly poorer physical and functional health, although, mental health and well-being scores were virtually identical for men and women.

### 1.2.3 The effect of rate control strategies on quality of life in atrial fibrillation patients

Six studies [112-117] have examined the effect of AV node/junction and bundle of HIS ablate and pace procedures, in paroxysmal AF, persistent and chronic AF patients. All these studies demonstrated a significant improvement in QoL over the post-intervention follow-up periods, which ranged from six weeks to 12-months (see Table 1.8).

Ten studies [118-127] have evaluated the effects of various rate control strategies on QoL in AF patients; eight comparing AV node/junction ablation and pacing [118-125] to AV modification [119-120], various modalities of pacing [118,124], against [125] or with the addition of pharmacological therapy post-intervention [121-123], and two [126-127] comparing ventricular rate control with drugs [126] or pacing [127]. Two studies [119-120] examining the effect of AV node ablation and pacing versus AV node modification report significant improvement in QoL in the ablate and pace group. The benefit of AV node modification on QoL is equivocal, with one study reporting no change in QoL for patients who had successful AV node modification [120], wheras the other reported significant improvement [119].

Permanent destruction of the AV node/junction and synchronous dual chamber/single chamber ventricular pacing is another rate control strategy in the management of refractory AF. Two studies [118,124] have examined the effect of various pacing strategies following ablation on QoL. Both single chamber pacing in chronic AF and dual chamber pacing in paroxysmal AF patients following ablation provided similar significant improvements in QoL [118], irrespective of whether rate responsive pacing was turned on or off [124]. The remaining four studies [121-123,125] have examined the effect of pharmacological rate control therapy, in addition to [121-123], and in comparison to [125], ablation and/or pacing procedures. Two studies demonstrated that adjunctive pharmacological therapy confers no additional benefit for QoL over and above ablation and pacing procedures alone [122,124]. However, Weerasooriya and colleagues [125] suggest that pharmacological rate control alone was as efficacious as AV junction ablation and pacing alone in improving QoL. Two studies comparing the effect of pacing and pharmacological therapy, with ablation and pacing with or without

drug therapy have also yielded conflicting results. One study found similar improvements in QoL under both rate-control regimes [122], whereas the other demonstrated no improvement in QoL in the group undergoing pacing with the addition of drug therapy [121]. The final two studies [126-127] examining the effects of ventricular rate control drugs [126] and pacing (without ablation) with or without ventricular response pacing [127], both reported no significant differences in QoL between groups following treatment.

### 1.2.4 The effect of rhythm control strategies on quality of life in atrial fibrillation patients

Fifteen studies have examined the effect of rhythm controlling strategies alone on QoL in AF patients using a number of different methods, including percutaneous [128-136] or surgical interventions [137-139], or internal/external cardioversion [140,142-143] and pacing [141] (see Table 1.9). Of the nine percutaneous intervention studies, four have used radio-frequency catheter ablation of atrial foci [128-130,133,136], and four [131-132,134-135] have employed pulmonary vein isolation, as rhythm control strategies for AF. All nine studies [128-136], assessing QoL with the SF-36, demonstrated significant improvements in QoL among these highly symptomatic patients following the intervention. Even unsuccessful PV isolation lead to increased QoL on half of the SF-36 subscales [136].

Three studies [137-139] have examined the impact of the Maze operation on QoL; one following mitral valve surgery [139]. QoL, again assessed by the SF-36, was significantly improved following the intervention [137-139], with AF patients reporting similar QoL scores to the general population [138]. However, the Maze operation, in

addition to mitral valve surgery, did not afford any additional enhancement in QoL, compared to mitral valve surgery alone [139].

Few studies [140-143] have examined the effect of cardioversion, atrial pacing or defibrillation, as rhythm control strategies on the QoL of AF patients. QoL is significantly improved among patients who have undergone DC cardioversion and remain in sinus rhythm [140], patients with an implanted atrial defibrillator [142-143], irrespective of the number of shocks applied [142], and patients with an implanted atrial septal pacemaker [141].

Only four studies to date [144-147] have compared the effects of two [145-146] or more [144,147] different rhythm controlling strategies on QoL. Two of these studies [145-146], comparing radio-frequency PV ablation to anti-arrhythmic drug therapy, revealed a better QoL in those patients receiving ablation, with little improvement in QoL among those treated pharmacologically. Of the other two studies [144,147], one compared the effects of short-term (8 weeks) and long-term (52 weeks) amiodarone therapy following successful DC cardioversion, with placebo and demonstrated a similar improvement in QoL in all three groups during the first year [147]. The other compared the effects of amiodarone, sotalol, or propafenone (with or without DC cardioversion) and found significant improvements in QoL in all three groups, but only for the first three months of follow-up [144].

### 1.2.5 The effect of rate- versus rhythm-control strategies on quality of life in atrial fibrillation patients

Eight studies have examined the effect of rate-control versus rhythm-control strategies on QoL in AF patients [148-155] (see Table 1.10). Five studies [148-152], including four large randomised trials, STAF [148], PIAF [149], RACE [150], and AFFIRM [152], compared pharmacological rate control with or without AV node ablation to cardioversion (DC or pharmacological) with or without pharmacological rhythm control. All reported an improvement in QoL following intervention. Of the four randomised trials, three [148-150] demonstrated a greater improvement in QoL, assessed using the SF-36, among patients receiving rate-control treatment. However, the AFFIRM trial [152] revealed that the improvement in QoL following intervention was similar for both rate- and rhythm-control strategies. The other study [151] to compare rate and rhythm strategies demonstrated that there was a significantly greater improvement in QoL among patients in the rhythm-control group. However, this study used a non-validated measure of QoL, in an uncharacteristically young AF population, and therefore caution is warranted in interpreting the results.

Three studies [153-155] have compared AV node/junction ablation with or without pacing to pharmacological therapy. All three studies, employing a variety of QoL assessments, demonstrated a significant increase in QoL in AF patients undergoing rate-control intervention compared to rhythm-control treatment [153-155].

## 1.3 Triggering of acute cardiovascular events

### 1.3.1 Background

Cardiovascular disease (CVD) remains the major cause of mortality and morbidity in the western world, with acute myocardial infarction (MI) accounting for a large percentage of the deaths observed [156]. The aetiology of MI is usually a chronic and multi-factorial process, with several risk factors, such as elevated serum cholesterol, hypertension, and smoking, being well recognised. In addition to established risk factors, it has been suggested that lifestyle and daily activities, such as psychological stress, postural adjustments and physical activity, may act as triggers for acute coronary syndromes (ACS).

The concept of 'triggering' emerged almost a century ago when Obraztsov and Strazhesko provided anecdotal evidence stating that 'direct events' (such as psychological stress or physical activity) could precipitate MI [157]. More robust evidence has subsequently emerged from self-report studies, demonstrating that in a population of patients who had experienced a MI nearly half (40-50%) reported one or more potential trigger, the most common being moderate/heavy physical activity, sudden change in position, and acute emotional upset [158-160].

Further support for the postural change triggering acute cardiovascular (CV) events is derived from research examining whether there is a morning excess in acute MI and sudden cardiac death. In 1985, a study by Muller and colleagues dispelled the long held opinion that acute CV events, such as myocardial infarction (MI), were completely random in nature [161]; there was an increased frequency between 6 a.m. and noon compared to the remaining 18 hours of the day [162]. Such findings sparked a great

deal of interest in the timing of cardiovascular events, and a number of retrospective and prospective studies subsequently demonstrated a morning excess in the onset of MI [163-164], sudden cardiac death [165-166], and transient myocardial ischaemia [167-168]. A resultant meta-analysis confirmed these findings, demonstrating a morning excess in acute MI and sudden cardiac death of 40% and 29%, respectively [169]. Indeed, further analysis revealed that the morning peak in acute CV events was more abrupt when time of awakening was taken into account. After adjusting for wake time, the incidence of sudden cardiac death in the 3 hours after awakening increased from 1.7 (95% CI, 1.0 – 2.8) to 2.6 (95% CI, 1.6 – 4.2) [170], observations that have also been replicated in MI patients [171-172]. Accordingly, it would be reasonable to hypothesize that the morning excess in acute CV events may result from the act of getting out of bed and commencing daily activities, and not be an intrinsic consequence of the morning period itself [173]. Although difficulty would arise in attempting attribute a specific external trigger (i.e. dehydration, physical exertion, mental stress) to the excess CV events in this period, it is possible that the assumption of an upright posture may be of significance.

Coronary plaque disruption and subsequent thrombosis is recognized as the underlying pathophysiological process marking the transition from stable coronary artery disease to ACS [174]. The exact mechanism of how psychological stress, assumption of an upright posture, and physical activity trigger this transition is still unknown. From current knowledge on thrombogenesis it is reasonable to postulate the increases in haemodynamic and mechanical sheer stress, reflected in increases in blood pressure, pulse rate, and cardiac contractility, in combination with increases in blood viscosity, could trigger plaque disruption, if circumstances were favourable. The next stage in the

transformation of a disrupted plaque to a 'clinically' active plaque involves the process of 'overlying' thrombosis. A number of studies have demonstrated an increase in platelet reactivity (aggregation and soluble markers) during implicated behavioural activities, which may play a significant role in the triggering of arterial thrombogenesis and eventual vessel occlusion.

### 1.3.2 Effects of acute psychological stress on haemorheology, coagulation, fibrinolysis and platelet reactivity

Laboratory studies examining the effect of acute psychological stress on haemorheology have focused on changes in blood viscosity and haemoconcentration. Findings from these studies demonstrate that the administration of a laboratory stress task of between 5 and 28 minutes duration can decrease plasma volume by up to 7 % [175-183], as well as increase in whole blood and plasma viscosity [178-180]. Only one study to date has reported no change in haematocrit following stress exposure [184].

A series of studies on healthy individuals by Veldhuijzen van Zanten and colleagues [177] demonstrated, in accordance with Ross et al. [178], that males exhibit an exaggerated stress-induced heamorheological stress response compared to age-matched females. Based on these findings, it has been speculated that this difference may, in part, contribute to the lower cardiovascular risk associated with pre-menopausal women.

Table 1.11 summarises the studies that have examined the effect of acute laboratory psychological stress tasks on haemostasis and platelet reactivity. Studies examining the effect of acute psychological stress on coagulation have in general yielded positive findings, demonstrating increases in clotting factors such as FVII:C, FVIII:C and

FXII:C [185-186], thrombin-antithrombin (TAT) complex [187,189-190], fibrinogen [186,188,196] and fibrin D-dimer levels [187,189-190]. Such results suggest that acute psychological stress affects biological processes at the beginning of both the intrinsic (FXII:C) and extrinsic (FVII:C) coagulation pathways, as well as in the final stages of the common pathway (fibrinogen and D-dimer). A study by von Kanel and colleagues demonstrated that prothrombin time (PT) and activated partial thromboplastin time (aPTT), more functional screening measures of coagulation, were unaffected by an acute stress task, suggesting that such measures may be too 'crude' to detect subtle changes in the cascade [186]. Research on fibrinolysis is far less conclusive, primarily due to the limited number of studies and the inconsistency of the findings. Work examining tissue-type plasminogen activator (t-PA), the molecule responsible for the degrading of fibrin into soluble fragments, is indicative of this inconsistency, with studies reporting increases [189,196], no change [193] and decreases follow acute psychological stress [187,199].

Studies examining the effect of acute stress on platelets have largely been concerned with alteration in platelet counts and secretion of platelet specific products, with a few earlier studies focusing on its effect on platelet aggregation. Results have generally shown that platelet count [190,196-197], the secretion of platelet specific products [192,200-201] and platelet aggregation [194-195,197,200,202] increases significantly following acute psychological stress. In contrast to Grignani and colleagues [202], Markovitz et al. found that platelet activation was significantly elevated following an acute stress task in healthy males, although no change was observed in coronary artery disease (CAD) patients [201]. Platelet responsiveness may also vary within a patient population [200]; WHO stage I hypertensive patients, although having comparable

levels of platelet aggregation and β-TG at baseline had an increased response to the stress task compared to normotensive controls. Interestingly, WHO stage II hypertensive patients showed no increase in platelet reactivity following the stress task although having elevated baseline parameters. To date, only one study [203] has used flow cytometric analysis to examine the platelet response to acute psychological stress and failed to demonstrate any significant changes in GPIbα and GPIIb/IIIα expression on the platelet membrane or any increases in fibrinogen binding index.

von Willebrand Factor (vWF), a protein of significant importance in haemostasis through its role in platelet-platelet and platelet-sub-endothelium adhesion, is the biochemical marker that has received the most attention in this context. The majority of studies have found significant increases following psychological stress exposure [185-186,189,196], possibly through increases in sheer stress leading to alterations in endothelium cell morphology and function.

### 1.3.3 Effects of acute change of posture on haemorheology, coagulation, fibrinolysis and platelet reactivity

To date, 20 studies have reported data on haemorheological change when an individual assumed an upright posture, predominately changes in haematoctrit [205,207-211, 213,215,217,220-221,226] and plasma volume [205-208,210,212,215,217-219,221-226]. Eleven studies reported absolute increases in haematocrit of between 1.3% to 4.6% [205,207-211,217,220-221,226], with two studies reporting relative changes in haematocrit between 7% and 8% [213-215] during postural challenges (head up tilt or upright standing) lasting between 15 and 120 minutes. The 15 studies examining acute changes in plasma volume report significant mean decreases of between 7% and 17%,

corresponding to a fluid loss of between 200 and 640 mL [205-207,210,212,215,217-219,221-226]. Four studies measured changes in haematocrit and/or plasma volume at multiple time points throughout the postural challenge [205-206,219,211]. Two of these studies demonstrated that the haemoconcentration was complete within 20 to 25 minutes [205,211], with Raj and colleagues reporting that 75% of the response was complete with the first five minutes of their head-up tilt protocol [206]. Sex differences in postural-induced haemoconcentration have received little attention. The two studies to date have produced conflicting findings, with one study reporting that men and women exhibited a similar haemorheological response [217] and the other demonstrating an exaggeration response in female participants [207].

One of the major factors determining an individual's orthostatic tolerance is their magnitude of blood volume [227], making it entirely plausible that intolerant individuals would demonstrate an exaggerated haemorheological response to acute changes in posture. Two [208,212] of the four studies [206,208,210,212] addressing this issue found that individuals with orthostatic intolerance displayed a greater decrease in plasma volume [208] and blood volume [212] compared to controls. Further, four studies have examined whether hypertensive [224,226] and nephrotic syndrome patients [221] differ from healthy controls, with one study examining whether age was a contributing factor [223]. Although nephrotic patients demonstrated a greater degree of haemoconcentration compared to healthy individuals [221], the studies on hypertensive [224,226] and elderly individuals were inconclusive [223].

Five studies have examined the effect of an acute change in posture on haemostasis and platelet reactivity [213-216,227]. Two of these studies examined the effect of standing

(>30 minutes) on whole blood platelet aggregation and the expression of various glycoproteins on the platelet membrane (flow cytometric) [211,213]. Although an increase in platelet count (approx. 15%) and platelet aggregation was demonstrated, no change in the surface expression of the activation-dependent antibodies (i.e. P-selectin, activated GPIIb/IIIa, vWF, fibrinogen) was detected [213]. *In vitro* experiments have also been conducted to examine whether the increase in platelet aggregation was due to the increase in haematocrit and/or platelet count accompanying the change in posture [213]. Platelet aggregation was significantly increased when whole blood samples were treated with platelet rich plasma, suggesting that the haemoconcentration and increased platelet count may partly explain the increased levels of platelet aggregation [213]. The only research to date examining soluble platelet markers demonstrated an increase in beta-thromboglobulin in a hypertensive group, however, no change in platelet factor-4 was observed [215]. Soluble coagulation and fibrinolytic markers have also received minimal attention, although increases in prothrombin fragments 1 + 2 [204], euglobulin clot lysis time [215], tissue-plasminogen activator [213,215] have been reported.

### 1.3.4 Effects of physical activity on haemorheology, coagulation, fibrinolysis and platelet reactivity

There is a paucity of research investigating the effects of acute physical activity on haemorheology, however the available evidence indicates a significant increase in haematocrit of between 1 and 10 % [228-236], which is associated with a significant increase in blood and plasma viscosity [229,234,236].

Table 1.13 summarises the studies that have examined the effects of acute low, moderate, and high intensity exercise on haemostasis and platelet reactivity.

#### 1.3.4.1 Low Intensity Exercise (< 55% $VO_2$ Max)

To our knowledge, only two studies have examined the haemostatic response to low intensity exercise, one conducted on female post-MI patients [238] and the other in physically active and inactive males [237]. Eriksson-Berg and colleagues demonstrated that although markers of coagulation (D-dimer, TAT) and endothelium dysfunction were unaffected by the exercise, fibrinolytic activity was increased through an increase in t-PA antigen and activity level [238]. Szymanski and colleagues [237] demonstrated that t-PA activity was elevated following 30-minutes of exercise in both physically active and inactive participants, and that this increase was significantly greater when the exercise was performed in the evening compared to the morning.

#### 1.3.4.2 Moderate Intensity Exercise (56 to 75% $VO_2$ Max)

Much of the research examining the effects of moderate intensity exercise has been conducted on patient populations, including stroke, metabolic syndrome, hypertensive and peripheral vascular disease (PVD) patients. Moderate intensity exercise has been observed to elicit changes in t-PA (antigen and activity) [243,245-246], although findings on its inhibitor, PAI-1, are inconsistent, with some studies reporting decreases [243,245] or no change [246] in activity levels, as well as increases [244] or no change [245-246] in antigen concentration. Drawing definitive conclusions from these studies is difficult, as they have often failed to employ adequate control groups [239-240,243,245], or have tested only a small numbers of participants [241,244-245]. Morris and colleagues [244] demonstrated that individuals with metabolic syndrome were hypofibrinolytic, both at rest and during exercise in comparison to healthy controls, which they suggested might play a part in increasing their acute thrombotic risk. Desouza et al. [246] suggested that this risk might not be uniform across patients

groups, finding no difference in the fibrinolytic response between hypertensive and normotensive males. The few studies examining the effect of moderate intensity exercise on coagulation and platelet reactivity have also produced inconsistent findings, with some studies demonstrating increases in platelet count [239], aggregation [239] and reactivity [240], while others demonstrate no change [241].

1.3.4.3 High Intensity Exercise (> 75% $VO_2$ Max & Incremental Exercise Tests)

Research examining high intensity exercise is more suggestive of the development of a prothrombotic state. A hyperfibrinolytic state has consistently been demonstrated following this type of exercise, with the majority of studies observing decreases in euglobulin clot lysis time [258,267,269,282,289], PAI-1 antigen [272,279,282] and activity [248,250,254,260,262] levels, as well as increases in t-PA antigen [248,250,255,260-262,265,275-277,279,282] and activity levels [248,254,258-260], plasminogen $\alpha_2$-antiplasminogen (PAP) complexes [253,275], and plasminogen activator activity (PAA) and activator-inhibitor complex [279].

Research examining the effect of high intensity or incremental exercise on coagulatory markers and indices have reported increases in D-dimer [275] fibrinogen [250,271-272], TAT complex [275,277-278], antithrombin III [250], $F_{1+2}$ [250,253,255,278] and an array of clotting factors [259,264,268,288], with subsequent decreases in PT [259,267] and aPTT [250,259,267].

Although high intensity exercise has been associated consistently with increases in platelet count, in the region of 10 to 40% [256], with a recent study demonstrating an increase in mean platelet volume (MPV) in a patient population [270], the results for

platelet function are still equivocal. High intensity exercise has been shown by some [248-249,256,263], but not all [258,281], to increase platelet aggregation to ADP, collagen, epinephrine, and sheer stress. Studies examining the secretion of plasma specific proteins have also produced inconsistent findings, with some investigators reporting increases [257,280,283-285,287], no changes [258,263,271-272,285-286,289], and differences between patients and healthy individuals [281,286-287]. Studies examining platelet responses using flow cytometric analysis, have provided some positive findings with reported increased expression of P-selectin, GPIb, GPIV and GPIIb/IIIa [249,253,261].

It would appear reasonable to assume that healthy and physically active individuals would exhibit a more unfavourable haemostatic profile following heavy exercise compared to sedentary and diseased individuals. Research examining whether patients exhibit an attenuated fibrinolytic response have yielded conflicting findings, with studies reporting no differences [275], an impaired fibrinolytic response [276,290], as well as an exaggerated fibrinolytic response in patients [277,279]. Similar inconsistencies have also been demonstrated in studies examining changes in coagulatory and platelet variables [270,274-275,283,285,287,289]. Studies examining whether an individuals level of physical activity can affect the haemostatic response to physical activity have provided much more conclusive evidence. The majority of studies to date have demonstrated that sedentary individuals or those performing little physical activity have an attenuated fibrinolytic response, in combination with exaggerated changes in coagulatory and platelet variables compared to trained individuals, or those engaged in high levels of physical activity [251,255,257,260-261,267].

## 1.4 Aims and objectives

This thesis aims to explore the psychosocial and psychophysiological characteristics of AF patients and their effect on the prothrombotic state and prognosis. The main objectives are to:

1. Determine the level of psychosocial impairment in patients with AF in comparision to a hypertensive disease control group.
2. Examine whether the psychological status of AF patients can predict future quality of life, cardiovascular morbidity, and mortality.
3. Determine the effects of acute psychological stress and postural change on haemorheology and markers of endothelial dysfunction and platelet activation in patients with AF, in comparision with hypertensive and health individuals.
4. Examine whether hydration status can attenuate an individual's haemodynamic, rheological, endothelial, and platelet reactivity to acute psychological stress and postural change.

Table 1.5: Studies examining whether depression is a predictor for cardiovascular events and mortality in patients with coronary heart disease

| Author, year, place | Participants (Mean ± SD age, years) | Female (%) | Follow-up (months) | Method of assessing depression (cut-off employed to indicate depression) | Outcome variables | Unadjusted results (95% CI) | Variables adjusted for | Adjusted Results (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Carney et al., 1988[45] USA | 52 patients with CAD (56.2) | 27 | 12 | DSM-III-R | All-cause mortality | All-cause mortality: OR 2.65 (0.21-31.46) | | |
| Schleifer et al., 1989[46] USA | 283 patients post AMI (63.7; 27-90) | 36 | 3 | Schedule for Affective disorders and Schizophrenia | CV-mortality | CV-mortality: OR 0.59 (0.20-1.74) | | |
| Ladwig et al., 1991[47] & 1994[48] Germany | 560 male patients post AMI (54; 29-65) | 0 | 12 | Zerssen Self Rating Scale (scores †) | CV mortality | CV mortality: OR 5.3 (1.42-19.69) | Age, social status, previous CV events, helplessness | CV mortality: HR 4.9 (1.11-21.59) |
| Frasure-Smith et al., & Lesperance et al., 1993[49], 1995a[50], 1995b[51], 1996[52] Canada | 222 patients post AMI (60; 24-88) | 22 | 6 | BDI (scores ≥ 10) | CV mortality<br>CV events | CV mortality: OR 6.24 (1.88-20.67)<br>CV events: OR 3.32 (1.69-6.53) | Previous MI, Killip class, PVCs | CV mortality: HR 4.29 (3.14-5.86)<br>CV events: HR 1.99 (0.92-4.31) |
| Jenkinson et al., 1993[53] UK | 1376 patients post AMI (59; 25-84) | 22 | 6, 12, 36 | 3 items in the psycho-social questionnaire of the ASSET study (scores †) | All-cause mortality | 6-month all-cause mortality: OR 1.0 (0.35—2.83)<br>12-month all-cause mortality: OR 1.0 (0.42-2.37)<br>36-month all-cause mortality: OR 0.9 (0.47-1.76) | | |
| Barefoot et al., 1996[54] & 2000[55] USA | 1250 patients with CAD (52; 46 – 58) | 18 | 15.2 | Zung SDS (scores ≥ 50) | CV mortality | CV mortality: OR 1.26 (1.07-1.48) | Severity of disease, treatment | CV mortality: HR 1.42 (1.14-1.76) |
| Denollet et al., 1996[56] Belgium | 303 patients with CAD (55; 31-79) | 12 | 84 | MBHI (scores †) | CV mortality | CV mortality: OR 2.69 (1.33-5.45) | | |
| Denollet et al., 1998[57] Belgium | 87 patients with CAD (55.1;41-65) | 7 | 96 | MBHI (scores ≥ 10 pessimism scale; scores ≥ 12 despair scale) | CV mortality | CV mortality: OR 7.46 (1.56-35.80) | | |
| Frasure-Smith et al., | 222 patients post | 22 | 18 | Modified DIS | CV mortality | CV mortality: | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1999[58]<br>Canada | AMI (60; 24-88) | | | | | OR 3.64 (1.32-10.04) | | |
| Frasure-Smith et al., & Lasperance et al., 1999[58], 2000[59], 2002[60]<br>Canada | 887-896 patients post AMI | 32 | 12, 60 | BDI (scores ≥ 10) | CV mortality | 12-month CV mortality:<br>OR 3.22 (1.65-6.31) | Age, smoking, non-Q-wave MI, LVEF, Killip class | 60-month CV mortality:<br>OR 3.16 (1.78-5.59) |
| Kaufmann et al., 1999[61]<br>USA | 331 patients post AMI (65; 28-92) | 34 | 6, 12 | DIS | All-cause mortality | 6-month all-cause mortality:<br>OR 2.46 (0.86-6.98)<br>12-month all-cause mortality:<br>OR 2.34 (1.18—4.65) | | |
| Irvine et al., 1999[62]<br>Canada | 634 patients post AMI (63.8±10.8) | 17 | 24 | BDI (scores ≥ 10) | Sudden cardiac death | | Previous MI, significant biological predictors (†) | Sudden cardiac death:<br>HR 2.45 (1.14-5.35) |
| Hermann et al., 2000[63]<br>Germany | 5017 patients referred for exercise tests (53.8±12.7) | 15 | 60-72 | HADS (scores ≥ 8 on depression subscale) | All-cause mortality | | Age, sex, previous MI, ECG | All-cause mortality:<br>HR 1.21 (1.04-1.42) |
| Mayou et al., 2000[64]<br>UK | 344 patients post AMI (30-79) | 27 | 6, 18 | HADS (scores ≥ 19) | All-cause mortality | 6-month all-cause mortality:<br>OR 1.60 (0.43-5.95)<br>18-month all-cause mortality:<br>OR 1.64 (0.64-4.20) | | |
| Welin et al., 2000[65]<br>Sweden | 275 patients post AMI (>65; 30-65) | 16 | 120 | Zung SDS (scores ≥ 40) and BDI (scores ≥ 10) | CV-mortality | CV mortality:<br>OR 3.54 (1.85-6.77) | Sex, smoking, LVEF, hypertension, hypercholesterolemia, social support | CV mortality:<br>HR 3.16 (1.38-7.23) |
| Connerney et al., 2001[66]<br>USA | 309 patients with CAD (63.1±10.1) | 33 | 12 | BDI (scores ≥ 10) Modified DSM-IV | CV mortality | CV mortality:<br>OR 2.31 (1.17-4.56) | | |
| Lane et al., 2001[67] & 2002[68]<br>UK | 288 patients post AMI (62.7±11.5) | 25 | 12,36 | BDI (scores ≥ 10) | CV mortality | 12-month CV mortality:<br>OR 1.15 (0.49-2.70)<br>36-month CV mortality:<br>OR 0.84 (0.37-1.91) | Non-adjusted | |
| Borowicz et al., 2002[69]<br>USA | 172 patients with CAD (63.4) | 22 | 60 | CES-D scale (scores ≥ 16) | CV mortality | CV mortality:<br>OR 2.29 (0.74-7.11) | | |
| Romanelli et al., 2002[70] | 153 patients post | 44 | 4 | BDI (scores ≥ 10) or | All-cause morality | All-cause mortality: | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| USA | AMI (65-93) | | | DSM-III-R | | OR 4.71 (1.67-13.31) | | |
| Shiotani et al., 2002[71] Japan | 1,042 patients post AMI (63±11) | 64 | 12 | Zung SDS (scores ≥ 40) | CV events | | Age, sex, smoking, severity of myocardial infarction, hypertension, diabetes | CV event: HR 1.41 (1.03-1.92) |
| Carney et al., 2003[72] USA | 766 patients post AMI (58.9) | 40 | 30 | DSM-IV | All-cause mortality | All-cause mortality: OR 2.8 (1.50-5.30) | Age, smoking, LVEF, diabetes, bypass surgery after MI | All cause mortality: HR 2.4 (1.20-4.70) |
| Lauzon et al., 2003[73] Canada | 550 patients post AMI (60) | 21 | 12 | BDI (scores ≥ 10) | All-cause mortality CV events | | Age, sex, smoking, previous AMI, diabetes, hypertension, | All-cause mortality: HR 1.3 (0.59-3.03) CV events: HR 1.4 (1.05-1.86) |
| Strik et al., 2003[74] The Netherlands | 318 males post AMI (58±11) | 0 | 41 | SCL-90 (scores ≥ 23 on depression subscale | CV events | | Age, LVEF, use of anti-depressants | CV events: HR 2.32 (1.04-5.18) |
| Steeds et al., 2004[75] UK | 131 patients post AMI (<75) | n.s | 32 | BDI (scores ≥ 12) | All-cause mortality | All-cause mortality: OR = 1.8 (0.56-0.60) | | |

AMI = acute myocardial infarction; BDI = Beck Depression Inventory; CAD = coronary artery disease; CES-D = Centre for Epidemiological Studies Depression scale; CV = cardiovascular; DIS = Diagnostic Interview Schedule; DSM-III-R/IV = Diagnostic Statistical Manuals versions III-revised & IV; ECG = electrocardiogram; HADS = Hospital Anxiety and Depression scale; LVEF = left ventricular ejection fraction; MBHI = Million Behaviour Health Inventory; MI = myocardial infarction; SCL-90 = 90-item Symptom Checklist; SDS = Self-rating Depression Scale; ≥ = greater than or equal to; † = not reported

Table 1.6: Studies examining whether anxiety is a predictor for cardiovascular events and mortality in patients with coronary heart disease

| Author, year, place | Participants (Mean ± SD age, years) | Female (%) | Follow-up (year) | Method of assessing anxiety (cut-off employed to indicate anxiety) | Outcome variables | Unadjusted results (95% CI) | Variables adjusted for | Adjusted results (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Ahern et al., 1990[78] USA | 353 patients post MI (†) | † | 12 | STAI (scores ≥40) | CV mortality | | Age, LVEF, previous MI | † |
| Denollet et al., 1998[79] Belgium | 87 patients post AMI with LVEF ≤50% (41-69) | 7 | 8 | STAI-S (scores ≥48) | CV mortality<br>CV event | CV-mortality:<br>OR = 3.7 (1.1-12.4)<br>CV event:<br>OR = 3.4 (1.2-9.6) | | |
| Hermann et al., 2000[65] Germany | 5017 patients (53.8±12.7) | 15 | 5 | HADS (scores ≥10 on anxiety scale subscale) | All-cause mortality | | Age, sex, previous MI, ECG | † |
| Mayou et al., 2000[66] UK | 344 patients post AMI (30-79) | 27 | 0.5, 1.5 | HADS (scores ≥10) | All-cause mortality | 6 & 18-month all-cause mortality:<br>† | Non-adjusted | |
| Lane et al., 2001[67] UK | 288 patients post AMI (62.7±11.5) | 25 | 1 | STAI (scores ≥10) | All-cause mortality<br>CV mortality | All-cause mortality:<br>OR = 0.99 (0.96-1.03) for state anxiety<br>OR = 0.98 (0.94-1.02) for trait anxiety<br>CV-mortality:<br>† | | |
| Frasure-Smith et al., 2003[80] USA | 896 patients post AMI (59.4±11.2) | 26 | 5 | STAI-S (scores ≥40) | CV mortality | CV-mortality:<br>OR = 1.21 (1.01-1.46) | All baseline characteristics and treatment variables | CV-mortality:<br>HR = 1.14 (0.93-1.38) |
| Strik et al., 2003[74] The Netherlands | 318 males post AMI (58±11) | 0 | 3.4 | SCL-90 (scores ≥ 12 on anxiety subscale) | CV events | | Age, LVEF, use of anti-depressants | CV events:<br>HR 3.01 (1.20-7.60) |
| Pfiffner et al., 2004[81] Switzerland | 222 inpatients following an AMI (56.2±6.4) | 0 | 7 | MAS (scores ≥24) | All-cause mortality | All-cause mortality:<br>OR = 1.19 (†) | | |

AMI = acute myocardial infarction; CV = cardiovascular; ECG = electrocardiogram; HADS = Hospital Anxiety and Depression scale; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SCL-90 = Symptom checklist-90-item; STAI = state-trait anxiety inventory; STAI-S = state anxiety; STAI-T = trait anxiety; ≥ = greater than or equal to; not specified = †

Table 1.7: Summary of non-interventional studies examining quality of life in AF patients

| Author, year, place | Study design (follow-up period) | Participants (mean ± SD age, years) | Measure of quality of life | Results | Study limitations |
|---|---|---|---|---|---|
| Dorian et al (2000)[107] Canada | Cross-sectional | 152 PAF pts. (52 ± 12) vs. 47 healthy controls (54 ± 14) vs. 69 PTCA pts. (62 ± 9) | ➢ SF-36 | ➢ AF pts. reported a significant ↓ QoL compared to healthy controls ($p<0.001$) and PTCA pts (†) | ➢ Fewer healthy controls than pts. |
| Paquette et al (2000)[108] USA | Prospective (12- months) | 170 AF pts. 62 women (68 ± 9) vs. 108 men (62 ± 11) | ➢ SF-36 | ➢ Men and women demonstrated similar MCS at baseline (48.0± 10.0 vs. 47.6±10.8); $p>0.05$)<br>➢ Women had significantly ↓ PCS at baseline compared to men (36.1±8.8 vs. 45.2±7.8; $p<0.01$)<br>➢ Women demonstrated a significant ↑in PCS only over 12-months follow-up (36.1±8.8 to 38.5±9.5; $p<0.05$)<br>➢ Men demonstrated a significant ↑in MCS only over 12-months follow-up (47.6±10.6 to 50.4±10.9; $p<0.05$) | ➢ Males and females not age matched<br>➢ No appropriate control group |
| Howes et al (2001)[109] USA | Prospective | 52 chronic male AF pts. (77 ± 7.2) vs. 48 males in SR (76 ± 6.4) | ➢ SF-36 | ➢ Pts. and controls had similar PCS (43.0±11.0 vs. 45.9±10.4; $p=0.24$) and MCS (52.5±9.6 vs. 55.3±8.4; $p=0.07$) | ➢ Small sample size |
| van den Berg et al (2001)[110] The Netherlands | Cross-sectional | 73 PAF pts. (54.1 ± 13.4) vs. age- and sex-matched healthy controls (45 – 55) | ➢ SF-36 | ➢ AF pts. had a significant ↓ QoL ($p<0.05$), except on pain subscale ($p=0.73$), compared to healthy controls | ➢ Small sample size |
| Kang et al (2004)[111] USA | Prospective | 81 newly diagnosed (<3 months) AF pts. (67.3) | ➢ SF-36 | ➢ PCS and MCS were significantly ↓ in AF patients than US general population (38.5±11.5 vs. 50.0 and 48.7±11.5 vs. 50.0; $p<0.05$, respectively) | ➢ Small sample size<br>➢ No control group<br>➢ Reported only mental and physical health summary scores |

AF = atrial fibrillation; MCS = mental component summary score on the SF-36; MI = myocardial infarction; PAF = paroxysmal atrial fibrillation; PCS = physical component summary score on the SF-36;PTCA = percutaneous transluminal coronary angioplasty; pts. = patients; QoL = quality of life; SD = standard deviation; SF-36 = Medical Outcome Survey Short Form-36; SR = sinus rhythm; ↑ = increased; ↓ = decreased; < = less than; < = greater than; † = p-value not reported

Table 1.8: Summary of studies examining the effect of rate control on quality of life in AF patients

| Author, year, place | Study design (follow-up period) | Participants (mean ± SD age, years) | Intervention | Measure of quality of life | Results | Study limitations |
|---|---|---|---|---|---|---|
| **Studies examining rate control strategies alone** | | | | | | |
| *AV node/ junction and bundle of HIS ablation + pacing* | | | | | | |
| Kay et al (1988)[112] USA | Prospective (6-weeks) | 12 PAF pts. (67) | Radio-frequency catheter ablation of AV junction and pacing | ➢ McMaster Health Index<br>➢ PGWB questionnaire | ➢ Significant ↑ in QoL (p=0.002) and well-being (p=0.001) following intervention | ➢ Small sample size<br>➢ No control group<br>➢ Short follow-up period |
| Natale et al (1996)[113] USA | Prospective (12- months) | 12 chronic AF pts. (69 ± 9) | Radio-frequency catheter ablation of AV junction and pacing | ➢ Customised questionnaire to assess physical functional capacity and well-being | ➢ Significant ↑ in well-being (p<0.001) post-intervention | ➢ Small sample size<br>➢ No control group<br>➢ Non-validated QoL instrument |
| Kay et al (1998)[114] USA<br><br>Ablate & Pace Trial | Prospective (12-months) | 156 chronic symptomatic AF pts. (61.1 ± 11.5) | Radio-frequency catheter ablation of bundle of HIS and permanent pacemaker implantation | ➢ Health status questionnaire<br>➢ QoL index – cardiac version III | ➢ Significant ↑ in QoL (p<0.001) on all 8 health status subscales post-intervention<br>➢ Significant ↑ in QoL from baseline to 3 months (p<0.05), with no further improvement at 12 months (p>0.05)<br>➢ Significant ↑in QoL index over time (20.4±4.7 to 23.0±5.2; p=0.0001) | ➢ Highly symptomatic pts.<br>➢ No control group |
| Marshall et al (1998)[115] UK | Prospective (6-weeks) | 18 PAF pts. (63) | Radio-frequency catheter ablation of AV node and pacemaker implantation | ➢ PGWB Questionnaire<br>➢ McMaster Health Index | ➢ Significant ↑ in QoL assessed by PGWB after intervention (59.4 to 77.2; p<0.01) | ➢ Small sample size<br>➢ Highly symptomatic pts.<br>➢ No control group |
| Levy et al (2000)[116] UK | Prospective (1-month) | 15 PAF pts. (62 ± 9) | Radio-frequency catheter ablation of AV node and pacemaker implantation | ➢ Modified Karolinska questionnaire | ➢ Significant ↑ in QoL after 1 month of pacing (59.0±24.0 to 36.0±24.0; p=0.001) | ➢ Small sample size<br>➢ Highly symptomatic pts.<br>➢ Short follow-up period<br>➢ No control group |
| Takahashi et al (2003)[117] Japan | Prospective (6 months) | 38 symptomatic PAF and persistent AF pts. (69 ± 12) | Radio-frequency catheter ablation of AV node and pacing | ➢ WHO-26 | ➢ Significant ↑ in QoL and general health (2.4±0.5 to 3.1±0.8; p<0.01) and physical health (2.8±0.8 to 3.5±0.8; p<0.01) post-ablation therapy | ➢ Small sample size<br>➢ No control group |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Studies comparing different rate control strategies** | | | | | | |
| (a) *AV node/junction ablation/modification ± pacing and/or pharmacological rate control* | | | | | | |
| Fitzpatrick et al (1996)[118] USA | Retrospective (2.3 ± 1.2 years) | 90 AF pts.: 36 PAF pts. (59 ± 12) and 54 chronic AF pts. (61 ± 16) | Radio-frequency catheter ablation of AV junction with single pacing in chronic AF pts. vs. radio-frequency catheter ablation of AV junction with dual chamber pacing in PAF pts. | ➢ Customised QoL questionnaire | ➢ Significant ↑ in QoL and ease of daily living post-intervention (1.9±1.2 to 3.6±1.1; p<0.001) | ➢ No control group<br>➢ Non-validated QoL instrument |
| Lee et al (1998)[119] Taiwan | Prospective, randomised (6-months) | 60 PAF/ permanent AF pts. (AV ablation group: 69 ± 9, AV junction modification group: 66 ± 10) | 30 pts. to AV junction ablation with permanent pacing vs. 30 pts. to AV junction modification | ➢ QoL diaries | ➢ Significant ↑ QoL in both the ablation (3.2±1.2 to 1.0±0.8; p<0.05) and modification groups (3.1±1.1 to 1.7±0.7; p<0.05) post-intervention<br>➢ Greatest ↑ in Qol in AV junction ablation and pacing group (p<0.05) | ➢ Non-validated QoL instruments |
| Twidale et al (1998)[120] USA | Prospective (4-weeks) | 44 chronic AF pts. with congestive heart failure (69.7 ± 10.2) | 22 pts. to radio-frequency catheter ablation of AV node and pacemaker implantation vs. 22 pts. radio-frequency catheter AV node modification | ➢ Minnesota LHFQ | ➢ Significant ↑ in QoL in AV node ablation and pacing group post intervention (66.1±22.6 to 36.9±17.1; p<0.01)<br>➢ No change in QoL for pts. who had successful AV node modification (p>0.05) | ➢ Highly symptomatic pts.<br>➢ Non-randomised<br>➢ Groups not age matched |
| Natale et al (1999)[121] USA | Prospective (6-months) | 75 chronic AF pts. (Group 1: 68.4 ± 7 Group 2: 69.2 ± 10.1 Group 3: 69.8 ± 11.3) | **Group 1:** AV node ablation, pacemaker implantation plus drug therapy<br>**Group 2:** AV node ablation, pacemaker implantation without drug therapy<br>**Group 3:** Pacemaker implantation and drug therapy | ➢ QoL enjoyment and satisfaction questionnaire<br>➢ Perception of well-being | ➢ Significant ↑ in QoL from baseline to 6-months for groups 1 (24±2.1 to 55±3.0; p<0.001) and 2 (22±2.0 to 30±4.6; p<0.001)<br>➢ Significant ↑in well-being from baseline to 6-months for groups 1 (1.2±0.3 to 3.1.1±0.4; p<0.001) and 2 (1.3±0.4 to 2.0±0.4; p<0.05)<br>➢ No change in QoL for group 3 (p>0.05) | ➢ Not randomised to treatment arms<br>➢ No placebo medication for pts. in Group 2. |
| Levy et al (2001)[122] UK | Prospective, randomised (12- months) | 36 permanent AF pts. (69 ± 7) | 18 pts. to Bundle of HIS ablation and permanent pacing vs. 18 pts. to permanent pacing and AV modifying drugs | ➢ Karolinska questionnaire<br>➢ Nottingham Health Profile | ➢ Baseline QoL similar in both groups (p>0.05)<br>➢ Significant ↑ in QoL in both groups post-intervention (p<0.05) | ➢ Small sample size |
| Brignole et al (2002)[123] Italy | Prospective, randomised longitudinal | 141 PAF pts. (Anti-arrhythmics group: 67 ± 8; no | AV junction ablation and pacing ± anti-arrhythmic drugs post-intervention | ➢ Minnesota LHFQ | ➢ Significant ↑ in QoL in both groups over time following intervention (p<0.05) | ➢ Heart failure-specific QoL instrument (although 27 pts. also had heart failure) |

| | | | | | | |
|---|---|---|---|---|---|---|
| PAF-2 trial | (12-months) | drug therapy group: 69 ± 8) | | | ➢ No differences in improvement in QoL between groups following intervention (p=0.54) | |
| Duff et al (2003)[124] Canada | Prospective (6-months) | 28 drug refractory AF pts | AV junction ablation and pacing with rate responsive mode on (n=14) or off (n=14) | ➢ SF-6<br>➢ Arrhythmia Syndrome Scale<br>➢ Ladder of Life | ➢ Significant ↑ QoL for both groups in 10/12 QoL questions (p<0.001)<br>➢ No significant differences in QoL between groups (p>0.05) | ➢ Small sample size<br>➢ Highly symptomatic pts. |
| Weerasooriya et al (2003)[125] Australia<br><br>AIRCRAFT | Prospective (12-months) | 99 permanent AF pts. (68 ± 8.6) | 49 pts. to AV junction ablation and pacing vs. 50 pts. to pharmacological ventricular rate control | ➢ AQoL<br>➢ CAST QoL Questionnaire | ➢ Significant ↑ in QoL on AQoL for both groups (p<0.05)<br>➢ Significant ↑ in QoL on CAST QoL questionnaire in AV junction ablation group (p<0.05) only | |
| (b) *Pharmacological rate control vs. pharmacological rate control* | | | | | | |
| Tse et al (2001)[126] Hong Kong | Prospective, randomised (6 months) | 16 chronic AF pts. (63 ± 9) | 7 pts. to digoxin vs. 9 pts. to amiodarone | ➢ SF-36 | ➢ No significant effect on QoL at follow-up for either groups (p>0.05) | ➢ Small sample size |
| (c) *Pacing alone* | | | | | | |
| Tse et al (2004)[127] Hong Kong | Prospective, randomised (6 weeks) | 38 PAF (74 ± 9) and 39 persistent AF pts (70 ± 11) | VVIR or DDDR pacemaker implantation with VRP on or off | ➢ SF-36 | ➢ No significant differences on any of the SF-36 subscales between VRP on or off groups (†) | ➢ Short-term follow-up period |

AF = atrial fibrillation; AIRCRAFT = Australian Intervention Randomised Control of Rate in Atrial Fibrillation Trial; AQoL = Assessment of Quality of Life; AV = atrio-ventricular; CAST = Cardiac Arrhythmia Suppression Trial; CTAF = Canadian Trial of Atrial Fibrillation; DC = direct current; LHFQ = Living with Heart Failure Questionnaire; PAF = paroxysmal atrial fibrillation; PAF-2 = Paroxysmal Atrial Fibrillation-2 trial; PGWB = Psychological General Well Being; pts. = patients; QoL = quality of life; SD = standard deviation; SF-6 = Medical Outcome Survey Form-6, SF-36 = Medical Outcome Survey Short Form-36; SR = sinus rhythm; VRP = ventricular response pacing; WHO-26 = World Health Organisation 26-item Questionnaire, ↑ = increased; ↓ = decreased; < = less than; > = greater than; † = p-value not reported.

Table 1.9: Summary of studies examining the effect of rhythm control on quality of life in AF patients

| Author, year, place | Study design (follow-up period) | Participants (mean ± SD age, years) | Intervention | Measure of quality of life | Results | Study limitations |
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| **Studies examining rhythm control strategies alone** | | | | | | |
| (a) *Percutaneous interventional studies* | | | | | | |
| Dierkes et al (2003)[128] Germany | Prospective (2.1 years) | 33 drug refractory PAF pts. (56.1 ± 9.9) | Radio-frequency catheter ablation of right atrial isthmus region | ➢ SF-36 | ➢ Significant ↑ QoL post-ablation ($p<0.05$) | ➢ No control group |
| Erdogan et al. (2003)[129] Germany | Prospective (33.9 ± 11 months) | 33 PAF pts. (54.1 ± 9.5) | Radiofrequency catheter ablation of atrial foci | ➢ SF-36 | ➢ Baseline QoL scores ↓ than age-matched general German population<br>➢ Successful ablation significantly ↑ QoL scores on 7/8 subscales ($p<0.05$)<br>➢ Non successful ablation significantly ↑ QoL in only 2/8 subscales ($p<0.05$) | ➢ No control group |
| Goldberg et al (2003)[130] USA | Prospective (36- months) | 33 PAF pts. (51 ± 18) | Radio-frequency catheter ablation of right atrial foci and PV | ➢ SF-36 | ➢ Significant ↑ in QoL on 7/8 subscales 12 months post-ablation ($p<0.05$), except bodily pain ($p>0.05$) | ➢ No control group |
| Nilsson et al (2003)[131] Denmark | Retrospective (6-months) | 30 PAF pts. (51 ± 9) | PV isolation | ➢ SF-36 | ➢ Significant ↓ QoL scores in 5/8 subscales prior to PV isolation compared to healthy population ($p<0.05$) and ↓ in 6/8 subscales compared to hypertensive pts. ($p<0.05$)<br>➢ Significant ↑ QoL scores in 7/8 subscales after PV isolation ($p<0.05$), except bodily pain ($p>0.05$) | ➢ Highly symptomatic pts.<br>➢ Retrospective study<br>➢ No control group |
| Tada et al (2003)[132] Japan | Prospective (6 ± 3 months). | 50 PAF pts. (58 ± 7) | Segmental PV isolation ± antiarrythmic drug therapy post intervention | ➢ SF-36 | ➢ Significant ↑in PCS and MCS post ablation therapy regardless of drug therapy ($p<0.001$) | ➢ No control group |
| Calo et al | Prospective | 74 | Radio-frequency catheter | ➢ SF-36 | ➢ QoL scores prior to ablation | ➢ Highly symptomatic pts. |

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| (2004)[133]<br>Italy | (3 months & every 3 months thereafter) | PAF/permanent AF pts. (57 ± 7) | ablation of multiple regions around the right atrium | | significantly ↓ than general population ($p<0.05$)<br>➢ Significant ↑ on all subscales of SF-36 post ablation ($p<0.001$) | ➢ No control group |
| Chen et al (2004)[134]<br>USA | Prospective (6-months) | 193 AF pts. with (55 ± 11) or without (57 ± 8) impaired systolic function | PV isolation | ➢ SF-36 | ➢ Significant ↑ QoL post PV isolation in all QoL domains for those without impaired systolic dysfunction ($p<0.05$) | ➢ Pts. not randomised<br>➢ No control group |
| Purerfellner et al (2004)[135]<br>The Netherlands | Prospective (6-months) | 75 AF pts. (53 ± 11) | PV isolation | ➢ SF-36 | ➢ Baseline QoL scores significantly ↓ than healthy controls and AF controls (previously published data) ($p<0.001$) except for physical functioning ($p=0.13$) and bodily pain ($p=0.39$)<br>➢ Significant ↑ in PCS (45.4±9.7 to 51.7±6.5; $p<0.0001$) and MCS (44.5±11.3 to 51.7±8.7; $p<0.0001$) | ➢ Recruited no control group<br>➢ Highly symptomatic pts. |
| Gerstenfeld et al (2001)[136]<br>USA | Prospective (6-months) | 30 PAF/persistent AF pts. (SR group: 52 ± 10; AF recurrence group: 48 ± 14) | Radio-frequency catheter of ablation of atrial foci ablation vs. electrophysiological mapping without ablation | ➢ Modified SF-36 | ➢ Significant ↑ in all QoL subscales in pts. who underwent mapping with ablation ($p<0.05$)<br>➢ Significant ↑ in health distress only in pts. who underwent mapping without ablation ($p<0.05$)<br>➢ Similar ↑ in QoL regardless of whether the procedure was a success or not ($p<0.05$) | ➢ Highly symptomatic pts. |
| (b) *Surgical interventional studies* | | | | | | |
| Jessurun et al (2000)[137]<br>The Netherlands | Prospective (12-months) | 41 PAF pts. (49 ± 8) | Maze operation | ➢ SF-36 | ➢ Significant impairment in QoL pre-surgery ($p<0.05$)<br>➢ Significant ↑ QoL in 6/8 subscales 3-months after successful operation, except bodily pain ($p=0.85$) and role limitation due to emotions ($p=0.09$)<br>➢ No significant ↑QoL from 3 to 12-months ($p>0.05$) | ➢ Small sample size (QoL only assessed in 18 pts.)<br>➢ No control group |

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| Lonnerholm et al (2000)[138] Sweden | Prospective (12-months) | 30 PAF/persistent pts. and 18 permanent AF pts. | Maze operation | ➢ SF-36 | ➢ Pre-surgery QoL significantly ↓ than general Swedish population (†)<br>➢ Significant ↑ in QoL at 6 and 12-months on all scales ($p<0.001$) except for bodily pain ($p=0.09$) | ➢ No control group |
| Jessurun et al (2003)[139] The Netherlands | Prospective, randomised (12-months) | 35 AF pts. (64) | Randomised 2.5:1 ratio to maze operation or no maze operation following MV surgery | ➢ SF-36 | ➢ Significant ↑ QoL post MV surgery ($p<0.05$)<br>➢ Maze operation post MV surgery did not ↑ QoL further ($p>0.05$) | ➢ Highly symptomatic pts. |
| (c) *Internal/external cardioversion and pacing studies* | | | | | | |
| Berry et al (2001)[140] UK | Prospective (12-months) | 111 persistent AF pts. (66.8 ± 11) | DC cardioversion | ➢ EuroQuoL visual analogue scale | ➢ Significant ↑ in QoL in pts. who remained in SR (+10.3±3.5%; P=0.01) | ➢ No control group |
| Kale et al 2002[141] UK | Prospective (<24-months) | 28 PAF pts. (58) | Atrial septal pacemaker implantation | ➢ Customised QoL questionnaire | ➢ 79% pts. reported some improvement in QoL at follow-up (†) | ➢ Highly symptomatic pts.<br>➢ No control group<br>➢ Non-validated QoL instrument |
| Newman et al (2003)[142] USA | Prospective (12 months & every 6 months thereafter) | 173 AF pts. vs. 269 healthy controls | Implanted atrial defibrillator | ➢ SF-36 | ➢ Baseline QoL significantly ↓ compared to healthy controls ($p<0.05$)<br>➢ Intervention significantly ↑ QoL on 5/8 subscales ($p<0.05$), irrespective of number of shocks applied | ➢ No control group<br>➢ Highly selected symptomatic pts. |
| Ricci et al (2004)[143] Italy | Prospective (15 ± 4 months) | 40 drug refractory AF pts. (64 ± 10) | Dual defibrillator implantation | ➢ SF-36 | ➢ Significant ↑ QoL after implantation ($p<0.05$)<br>➢ Early delivery of atrial shock led to greater improvement in QoL (†) | ➢ No control group |
| **Studies comparing various rhythm control strategies** | | | | | | |
| (a) *Rhythm control vs. rhythm control* | | | | | | |
| Dorian et al (2002)[144] Canada<br><br>CTAF trial | Prospective, randomised (3 & 12 months) | 294 PAF or persistent AF pts. (65 ± 10) | 50% on amiodarone vs. 25% on sotalol vs. 25% on propafenone (+ DC cardioversion if needed) | ➢ SF-36 | ➢ Significant ↑ QoL from baseline to 3 months in all three groups ($p<0.05$)<br>➢ No significant between group differences in QoL ($p>0.05$)<br>➢ No significant changes in QoL | |

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| | | | | | between 3 and 12 months follow-up (p>0.05)<br>➢ No significant differences in QoL at 3 months between those cardioverted or not (p>0.05) | |
| Krittayaphong et al (2003)[145]<br>Bangkok | Prospective, cross-sectional<br>(12 months) | 38 symptomatic AF pts.<br>(ablation group: 55.3 ± 10.5; drug therapy: 48.6 ± 15.4) | 15 pts. to radio-frequency catheter ablation therapy of left atrium and PV vs. 15 pts. to amiodarone | ➢ SF-36 | ➢ Significant ↑ QoL in ablation group (p=0.007)<br>➢ No improvement in QoL in amiodarone group (p=0.86) | ➢ Small sample size<br>➢ Highly symptomatic pts. |
| Pappone et al (2003)[146]<br>Italy | Prospective<br>(12 months & every 6 months thereafter) | 211 AF pts.<br>(65 ± 10) | 109 pts. to radio-frequency PV ablation vs. 102 pts. to anti-arrhythmic drug therapy | ➢ SF-36 | ➢ Baseline QoL similar in both groups (p>0.05)<br>➢ Significant ↑ QoL in ablation group (p<0.05); QoL at normative levels by 6-months (p=0.004), no further changes at 1 year (p>0.05)<br>➢ Little improvement in QoL in medically treated group over 12-months (†) | ➢ Not randomised to treatment<br>➢ Highly selected symptomatic patients<br>➢ QoL data available on only 18% of total study population |
| Channer et al (2004)[147]<br>UK | Prospective, randomised, placebo controlled<br>(12 months) | 161 persistent AF pts.<br>(Placebo: 68 ± 8, Short-term amiodarone: 65 ± 10, Long-term amiodarone: 66 ± 10) | **Placebo:** Placebo for 2 weeks prior to and 52 weeks after successful DC cardioversion<br>**Short-term amiodarone:** Amiodarone for 2 weeks prior to and 8 weeks after successful DC cardioversion, followed by placebo for 44 weeks<br>**Long-term amiodarone:** Amiodarone for 2 weeks prior to and 52 weeks following successful DC cardioversion | ➢ SF-36 | ➢ Similar QoL scores in all three groups at baseline (†)<br>➢ Similar ↑ in QoL in all three groups at 8 and 52 weeks follow-up (†) | ➢ Placebo group not sex-matched with two amiodarone groups |

AF = atrial fibrillation; AV = atrio-ventricular; CTAF = Canadian Trial of Atrial Fibrillation; DC = direct current; EuroQoL = EuroQoL visual analogue scale; LHFQ = Living with Heart Failure Questionnaire; MCS = mental component summary score on SF-36; MV = mitral valve; PAF = paroxysmal atrial fibrillation; PGWB = Psychological General Well-Being; pts. = patients; PCS = physical component summary score on SF-36; PV = pulmonary vein; QoL = quality of life; SD = standard deviation; SF-36 = Medical Outcome Survey Short Form-36; SR = sinus rhythm; ↑ = increased; ↓ = decreased; < = less than; > = greater than; † = no p-value reported.

Table 1.10: Summary of studies examining the effect of rate vs. rhythm control on quality of life in AF patients

| Author, year, place | Study design (follow-up period) | Participants (mean ± SD age, years) | Intervention | Measure of quality of life | Results | Study limitations |
|---|---|---|---|---|---|---|
| (a) *Pharmacological rate control ± AV node ablation vs. cardioversion (DC or pharmacological) ± pharmacological rhythm control* | | | | | | |
| Carlson et al (2003)[148] Germany<br><br>STAF | Prospective, randomised (36- months) | 200 persistent AF pts. | **Rate:** beta-blockers, digitalis, calcium antagonists<br><br>**Rhythm:** Serial cardioversion, antiarrhythmic drugs or beta-blocker | ➢ SF-36 | ➢ Significant ↓ QoL in AF pts. compared to healthy age-matched controls in SR (from previous research) ($p<0.01$)<br>➢ Significant ↑ in 2/8 subscales in rhythm control group ($p<0.05$) vs. 5/8 in rate control group ($p<0.05$) | ➢ Two groups not sex-matched<br>➢ Poorer QoL baseline scores in rate control group<br>➢ No placebo group |
| Gronefeld et al (2003)[149] Germany<br><br>PIAF trial | Prospective randomised (12- months) | 252 persistent AF pts. (60.5) | **Rate:** Pharmacological ventricular rate control or AV node ablation<br><br>**Rhythm:** Pharmacological or electrical cardioversion | ➢ SF-36 | ➢ No significant differences in baseline QoL between rate and rhythm group ($p>0.05$)<br>➢ Significant ↓ QoL in AF pts. compared with healthy individuals ($p<0.05$)<br>➢ Significant ↑ in 6/8 and 5/8 QoL domains for rate ($p<0.05$) and rhythm control group ($p<0.05$), respectively | ➢ Significantly more pts. in rhythm control arm were newly diagnosed<br>➢ No placebo group |
| Hagens et al (2004)[150] The Netherlands<br><br>RACE trial | Prospective, randomised (36- months) | 352 persistent AF pts. (68 ± 9) | **Rate:** Rate controlling drugs and oral anticoagulation<br><br>**Rhythm:** Serial DC cardioversion, anti-arrhythmic drugs and oral anticoagulation | ➢ SF-36 | ➢ Significant ↓ QoL in AF pts. at baseline compared to healthy controls ($p<0.05$), but similar for rhythm and rate control ($p>0.05$)<br>➢ Rate control group ↑ significantly in 3/8 domains (role physical, mental health, and social functioning; $p<0.05$)<br>➢ Rhythm control group did not show a significant improvement in any QoL domain ($p>0.05$) | ➢ Two groups were not sex-matched<br>➢ No placebo group |
| Vora et al. (2004)[151] India (49) | Cross-sectional (12-months) | 144 chronic AF pts. (38.6 ± 10.3) | **Rate:** 48 pts. randomised to receive 90 mg of diltiazem twice daily to maintain resting ventricular rate <130 beats/min<br><br>**Rhythm:** 48 pts. to amiodarone<br><br>**Control:** 48 pts. to placebo | ➢ Unspecified QoL instrument | ➢ Significantly greater ↑ in QoL in rhythm control group than rate control group (†)<br>➢ Sub-group analysis revealed that whether or not the pts. remained in SR at follow-up predicted QoL (†) | ➢ Non-specified/non-validated QoL instrument<br>➢ Very young AF group |

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| Jenkins et al (2005)[152]<br><br>AFFIRM trial | Prospective, randomised (72-months) | 716 PAF and chronic AF pts. (70 ± 9) | **Rate:** Rate controlling drugs and oral anticoagulation<br><br>**Rhythm:** Serial DC cardioversion, anti-arrhythmic drugs and oral anticoagulation | ➢ SF-36<br>➢ QoL Index (Cardiac Version)<br>➢ Cantril Ladder of Life | ➢ QoL was similar in both treatment groups at baseline (p>0.05)<br>➢ Significant ↑ in QoL from baseline to follow-up in both groups (p<0.05)<br>➢ Similar ↑ in QoL for both groups (p>0.05) | |
| (b) *AV node/junction and bundle of HIS ablation ± pacing vs. pharmacological therapy* | | | | | | |
| Brignole et al (1997)[153]<br>Italy | Prospective, randomised (6-months) | 43 severely symptomatic PAF pts. (ablation group: 66 ± 10, medical group: 64 ± 10) | **Rate:** 22 pts. to AV junction ablation and pacing<br><br>**Rhythm**: 21 pts. to anti-arrhythmic drug therapy | ➢ Minnesota LHFQ | ➢ Greater ↑ in QoL and ↓ in symptoms in ablate and pace group (50±19 to 20±16; p<0.0001) compared to anti-arrhythmic group (50±19 to 43±22; p=0.0006) | ➢ Highly selected symptomatic pts.<br>➢ Heart failure-specific QoL instrument employed |
| Marshall et al (1999)[154]<br>UK | Prospective, randomised (18-weeks) | 56 symptomatic PAF pts. (ablate and pace group: 65 2 ± 7.5, medical group: 60.3 ± 9.8) | **Rate:** 37 pts. to AV junction ablation and pacemaker implantation<br><br>**Rhythm:** 19 pts. to medical therapy | ➢ PGWB questionnaire<br>➢ McMaster Health Index | ➢ Similar baseline scores on PGWB questionnaire and McMaster Health index (p>0.05)<br>➢ Significant ↑ in QoL in ablate and pace group from baseline to 18-weeks (PGWB: 68.8±18.1 to 77.4±21.6; p<0.05 and MHI: 14.8±3.3 to 16.1±3.2; p<0.05)<br>➢ No change in QoL for medical therapy group from baseline to 18-weeks (PGWB: 69.48±14.3 to 68.5±13.6; p>0.05 and MHI: 15.5±3.7 to 15.7±3.0; p.0.05) | ➢ Highly selected and symptomatic pts. |
| Ueng et al (2001)[155]<br>Taiwan | Prospective, cross-sectional (12-months) | 50 chronic lone AF pts. (ablation group: 68 ± 6, medical group: 65 ± 8) | **Rate**: 21 pts. to radio-frequency catheter ablation of AV junction and pacemaker implantation<br><br>**Rhythm:** 29 pts. to medical therapy | ➢ Detailed QoL diary | ➢ Medically treated showed no change in QoL (2.7±0.6 to 2.8±0.7; p>0.05)<br>➢ Significant ↑in QoL in ablate and pace group (2.8±0.6 to 2.1±0.5; p<0.05) | ➢ Non-validated QoL instrument<br>➢ Pts. not randomised to treatment |

AF = atrial fibrillation; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; AV = atrio-ventricular; AF = atrial fibrillation; DC = direct current; LHFQ = Living with Heart Failure Questionnaire; MHI = McMaster health index; PAF = paroxysmal atrial fibrillation; PGWB = Psychological General Well Being; PIAF = Pharmacological Intervention in Atrial Fibrillation trial; pts. = patients; QoL = quality of life; RACE = RAte Control versus Electrical cardioversion trial; SD = standard deviation; SF-36 = Medical Outcome Short Form-36; SR = sinus rhythm; STAF = Strategies of Treatment of Atrial Fibrillation; ↑ = increased; ↓ = decreased; < = less than; > greater than; † = no p-value reported

Table 1.11: Summary of the studies examining the haemostatic and platelet response to acute psychological stress

| Author, year, place | Participants (Mean ± SD age, years) | Study Design | Stress Task | Measurements | Results | Study limitation |
|---|---|---|---|---|---|---|
| *Healthy Participants Studies* | | | | | | |
| Zgraggen et al., 2005 Switzerland[185] | 22 healthy males (47 ± 0.8) | ➢ 1 visit<br>➢ 30 mins seated rest followed by a 13 mins stress task | ➢ TSST | ➢ Tissue Factor<br>➢ vWF antigen<br>➢ D-dimer<br>➢ Fibrinogen<br>➢ FVII:C activity<br>➢ FVIII:C activity<br>➢ FXII:C activity | ➢ FVII:C, FVIII:C, and FXII:C activity and vWF all significantly ↑ following the stress task | ➢ No females included<br>➢ No recovery period<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| von Kanel et al., 2004 Switzerland[186] | 24 healthy males (47.1 ± 7.4) | ➢ 2 visits (approx. 2 week apart)<br>➢ 30 mins seated rest, 13 mins stress task, and 105 mins recovery | ➢ TSST | ➢ vWF antigen<br>➢ Fibrinogen<br>➢ FVII:C activity<br>➢ FVIII:C activity<br>➢ FXII:C activity<br>➢ D-dimer<br>➢ aPTT<br>➢ PT | ➢ vWF, fibrinogen, FVII:C, FXII:C all ↑ significantly during the task and ↓ during recovery<br>➢ D-dimer, FVIII:C, aPPT and PT showed no significant change during stress task<br>➢ No stress induced habituation to the task | ➢ No females included<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| von Kanel et al., 2004 Switzerland[187] | 48 elderly participants (71 ± 9) | ➢ 1 visit<br>➢ 15 mins seated rest, 9 mins stress task, and 14 mins recovery | ➢ Two standardised speech stress tasks where participant was accused of shoplifting | ➢ TAT antigen<br>➢ vWF antigen<br>➢ D-dimer<br>➢ t-PA antigen<br>➢ PAI-1 antigen | ➢ TAT and D-dimer significantly ↑ following the stress task<br>➢ t-PA significantly ↓ following the stress task<br>➢ PAI remained unaltered by stress task | ➢ Short recovery period<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Steptoe et al., 2003 UK[188] | 125 men and 96 women (45 – 59) | ➢ 1 visit<br>➢ 30 mins rest, 10 mins stress task, and 45 mins recovery | ➢ Computerised SCW Test<br>➢ Mirror tracing task | ➢ Fibrinogen | ➢ Fibrinogen levels significantly ↑ during the stress task and remained elevated over the 45 mins recovery | ➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| von Kanel et al., 2003 Switzerland[189] | 37 care givers (72 ± 6) | ➢ 1 visit<br>➢ 20 mins seated rest followed by two 9 mins stress tasks | ➢ 1 task involved being falsely accused of shoplifting<br>➢ 1 task was an upsetting event related to care giving | ➢ TAT<br>➢ D-dimer<br>➢ t-PA antigen<br>➢ PAI-1 antigen<br>➢ vWF antigen | ➢ TAT, D-dimer, vWF and t-PA antigen all significantly ↑ following the stress tasks | ➢ No recovery period<br>➢ Failed to correct alterations in coagulatory markers for Δ plasma volume<br>➢ Failed to control for female menstrual cycle |
| von Kanel et al., | 19 participants | ➢ 1 visit | ➢ Speech stress | ➢ TAT | ➢ TAT and D-dimer significantly ↑ | ➢ Small sample size |

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| 2002<br>Switzerland[190] | (39 ± 5) | ➢ 30 mins seated rest, 6 mins stress task, 15 mins rest, and 3 mins stress task | task<br>➢ Mirror tracing task | ➢ D-dimer | following stress task<br>➢ Δ TAT significantly correlated with $\beta_2$-adrenoreceptor, Δ norepinephrine, and Δ epinephrine | ➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume<br>➢ Failed to control for female menstrual cycle |
| Mundal et al, 1996<br>Norway[191] | 26 healthy male controls | ➢ 1 visit<br>➢ Supine rest, 5 mins mental stress task followed by 15 mins recovery | ➢ Time-pressured mental arithmetic | ➢ Platelet count<br>➢ β-TG | ➢ Platelet count significantly ↑ during stress task, whereas β-TG demonstrated no change | ➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume<br>➢ Mental stress task too soon after CPT |
| Patterson et al., 1995<br>USA[192] | 27 healthy males (32 ± 8) | ➢ 1 visit<br>➢ 22 participants given stress intervention vs. 5 participants given no intervention (control)<br>➢ 30 mins supine rest, 10 mins mental stress, 30 mins recovery | ➢ Time pressured mental arithmetic task | ➢ PF-4<br>➢ β –TG | ➢ PF-4 and β-TG significantly ↑following the stress task<br>➢ ↑in β-TG was positively correlated with ↑ in norepinephrine | ➢ No females included |
| Jern et al., 1994<br>Sweden[193] | 11 healthy males (27.3; 22 – 36) | ➢ 1 visit<br>➢ 60 mins rest, 10 mins stress task followed by 20 mins recovery | ➢ Time pressured mental arithmetic task | ➢ t-PA antigen<br>➢ PAI-1 antigen | ➢ t-PA and PAI-1 antigen exhibited no change following the mental stress task | ➢ No females included<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Malkoff et al., 1993<br>USA[194] | 40 healthy male participants (21.4) | ➢ 1 visit<br>➢ 30 mins rest and 21 mins stress task or 21 mins more seated rest | ➢ SCW Task | ➢ Platelet aggregation<br>➢ Platelet secretion of ATP | ➢ Platelet secretion of ATP significantly ↑ during the stress task<br>➢ No change in platelet secretion of ATP in those with continued rest<br>➢ ADP-induced platelet aggregation demonstrated no significant change during the stress task | ➢ No recovery period<br>➢ No females included |
| Naesh et al., 1993<br>Denmark[195] | 8 healthy males (22 – 42) | ➢ 1 visit<br>➢ 30 mins rest, 20 mins stress task followed by 60 mins recovery | ➢ SCW Test | ➢ Platelet count<br>➢ Platelet aggregation<br>➢ β-TG<br>➢ PF-4<br>➢ ECLT | ➢ No significant change in platelet count following stress task<br>➢ No change in β-TG and PF-4 following stress task but significant ↑at 30 and 60 mins recovery<br>➢ No change in ADP-induced platelet aggregation during stress task but significant ↑at 30 mins recovery<br>➢ Significant ↓ in ECLT following stress task which remained ↓during recovery | ➢ Small sample<br>➢ No females included<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Jern et al., | 9 healthy women | ➢ 2 visits: 1 in follicular | ➢ SCW Test | ➢ Platelet count | ➢ Significant ↑ in platelet count and vWF | ➢ Small sample size |

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| 1991<br>Sweden[196] | (28: 24 – 30) | phase and 1 in luteal phase of menstrual cycle<br>➢ 30 mins seated rest, 2 x 10 mins stress tasks, followed by 10 mins recovery | ➢ Time pressured mental arithmetic task | ➢ FVII:C antigen and activity<br>➢ vWF antigen<br>➢ Fibrinogen<br>➢ t-PA antigen and activity<br>➢ PAI activity | at rest in follicular phase compared to luteal phase<br>➢ Significant ↑ in fibrinogen following stress task; change > in luteal phase<br>➢ Significant ↑ in vWF, t-PA antigen and activity following stress task; no differences between the two phases of menstrual cycle | ➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Larsson et al., 1990<br>Netherlands[197] | 8 healthy males (24 – 38) | ➢ 1 visit<br>➢ 30 mins rest, 17 – 25 mins stress task, followed by 60 mins recovery | ➢ SCW Test | ➢ Platelet count<br>➢ Platelet aggregation | ➢ Significant ↑ in platelet count following stress task<br>➢ Platelet aggregation significantly ↑ by 31% following stress task | ➢ Small sample size |
| *Patient Population Studies* | | | | | | |
| Strike et al., 2004<br>UK[198] | 17 male CAD pts. (52.8 ± 4.5) and 22 male healthy controls (50.2 ± 5.0) | ➢ 1 visit<br>➢ 30 mins rest, 10 mins stress task, and 120 mins recovery | ➢ Computerised SCW test<br>➢ Mirror tracing task | ➢ PLA | ➢ % of PLA ↑ significantly in both groups during the stress task<br>➢ % of PLA remained elevated during recovery in the CAD group but returned to baseline levels in healthy controls | ➢ No females included |
| Hevey et al., 2000<br>Ireland[199] | 11 post CABG patients (61.8 ± 5.7) | ➢ 2 visits<br>➢ Rest, followed by stress task | ➢ 1 visit: SCW test and PASAT test<br>➢ 1 visit: relaxation | ➢ t-PA/PAI-1 complexes<br>➢ t-PA antigen | ➢ t-PA and t-PA/PAI-1 complexes significantly ↓ following the stress task | ➢ Small sample size<br>➢ No control group<br>➢ No females included<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Tomada et al 1999<br>Japan[200] | 24 hypertensive patients, WHO stage I (40 ± 4) and WHO II (49 ± 3) vs. 14 normotensives (42 ± 4) | ➢ 1 visit<br>➢ 60 mins supine rest followed by 10 mins mental stress test | ➢ Time-pressured mental arithmetic | ➢ Platelet aggregation<br>➢ β –TG | ➢ Normotensive individuals demonstrated no significant changes following the stress task<br>➢ WHO Stage I hypertensives had similar baseline aggregation and β –TG to normotensive individuals but demonstrated a significant ↑in platelet aggregation and β –TG following the stress task<br>➢ WHO Stage II hypertensives had ↑baseline platelet aggregation and β –TG but demonstrated no change following the stress task | ➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume<br>➢ No recovery period |
| Markovitz et al., 1996<br>USA[201] | 14 post-MI patients (54.9) vs. 15 healthy male controls (53.5) | ➢ 1 visit<br>➢ 30 mins rest, two stress tasks followed by 10 mins recovery | ➢ Structured interview followed by 4 mins speech task | ➢ β –TG | ➢ β-TG significantly ↑ following stress tasks in healthy controls but showed no change in post-MI patients<br>➢ ↑ in β-TG was correlated with ↑ in hostility | ➢ No females<br>➢ Failed to correct alterations in coagulatory markers for |

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| | | | | | and type A behaviour scores | Δ in plasma volume |
| Grignani et al., 1991 Italy[202] | 25 post-MI patients (51 ± 8) vs. 10 healthy controls (51 ± 8) | ➢ 1 visit<br>➢ 30 mins rest, 10 mins stress task followed by a variable recovery time | ➢ Time pressured mental arithmetic task | ➢ Platelet aggregation<br>➢ $TxB_2$ | ➢ Significant ↑in platelet aggregation and $TxB_2$ following stress task. These effects were rapidly reversible<br>➢ Effects were more pronounced in post-MI patients than healthy controls | ➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |

ADP = Adenosine Diphospate, ATP = Adenosine Triphosphate, β-TG = Beta Thromboglobulin, CABG = Coronary Artery Bypass Graft, CAD = Coronary Artery Disease, CPT = Cold Pressor Test, ECLT = Euglobulin Clot Lysis Time, FVII:C = Clotting Factor VII, FVIII:C = Clotting Factor VIII, FXII:C = Clotting Factor XII, Mins = minutes, MI = Myocardial Infarction, PASAT = Paced Auditory Serial Arithmetic Task, t-PA = tissue-type Plasminogen activator, PAI -1 = Plasminogen Activator Inhibitor, PF-4 = Platelet Factor-4, PLA = Platelet-Leukocyte Aggregates, aPTT = activated Partial Thromboplatin Time , PT = Prothrombin Time, SCW = Stroop Colour Word, TAT = Thrombin-Antithrombin, $TxB_2$ = Thromboxane $B_2$, TSST = Trier Social Stress Test, vWF = von Willebrand Factor, WHO = World Health Organisation,↑ = increased , ↓ = decreased, Δ = change

Table 1.12: Haemorheological, haemostatic and platelet response to postural change (Supine to upright)

| Author, year, place | Participants (Mean ± SD age, years) | Study Design | Measurements | Results |
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| Jacob et al, 2005 USA[205] | 28 healthy individuals (33.6±8.0) | ➢ Supine rest overnight<br>➢ 30 min HUT ($60^0$) in 18 participants & 60 min unsupported standing in 10 participants<br>➢ Measured taken at min 2.5, 5, 7.5, 10, 15, 20, 30, 45 & 60 (when applicable) | ➢ Hct<br>➢ PVol (radio-labelled albumin/EB dye)<br>➢ Δ PVol (Hct/Hb method) | ➢ Hct ↑ 4.1<br>➢ PVol ↓ by 417 mL (6-25%)<br>➢ Haemoconcentration was complete within 20 mins of standing, with most occurring within the first 10 - 15 min |
| Raj et al., 2005 USA[1206] | 15 patients with POTS (36±11.0) and 14 healthy controls (34±7.0) | ➢ 60 min supine rest<br>➢ 30 min HUT ($60^0$)<br>➢ Measurements taken at min 5 and 30 | ➢ PVol (radio-labelled albumin)<br>➢ Δ PVol (Hct/Hb method) | ➢ PVol ↓ by 432 mL (15.3%) and 390 mL (16.6% ) at the end of tilt in control and POTS patients, respectively (NS)<br>➢ Combined data demonstrated an 11.05% ↓ after 5 min & a 15.9% ↓ after 30 min (NS) |
| Veldhuijzen et al., 2005 UK[207] | 24 healthy males (21.0±1.1) | ➢ 44 min supine rest<br>➢ 12 min HUT ($64^0$) | ➢ Hct<br>➢ Δ PVol (Hct/Hb method) | ➢ Hct ↑ Approx. 3%<br>➢ PVol ↓ Approx. 7% |
| Lagi et al., 2003 Italy[208] | 50 recurrent fainters (27; 18-41) vs. 37 healthy individuals (29; 18-43) | ➢ Unspecified supine rest<br>➢ 45 min HUT ($60^0$)<br>➢ Measurements take at min 10 | ➢ Hct<br>➢ Δ PVol (Hct/Hb method) | ➢ Hct ↑ 2.5% and 1.3% in recurrent fainters and controls, respectively<br>➢ PVol ↓ 17.1% and 8.6% in recurrent fainters and controls, respectively<br>➢ Females demonstrated a greater change in Hct with respect to male controls (3.5% vs. 2.6%, respectively) |
| Laszlo et al., 2001 Czech Republic[209] | 7 healthy males (24-38) | ➢ 40 min supine rest<br>➢ 30 min HUT ($0^0$,$12^0$,$30^0$,$53^0$,$70^0$)<br>➢ Measurements taken at 20 min and 40 min during supine rest, throughout the 30 min tilt, and up to 20 min after tilt | ➢ Hct | ➢ Hct ↑ by 0.3, 1.1, 2.7, and 3.2% at angles $12^0$,$30^0$,$53^0$,$70^0$, respectively |
| Gabbett et al., 2000 Australia[210] | 12 males with orthostatic hypotension (68±1) vs. 12 healthy male controls (69±1) | ➢ 20 min supine rest<br>➢ ≥15 min HUT ($90^0$) | ➢ Hct<br>➢ PVol (Δ Hct/Hb method) | ➢ Hct ↑ 2.5% in both the hypotensive and healthy control group<br>➢ PVol ↓ 9.2% and 8.3% in the hypotensive group and healthy control group (NS) |
| Andrews et al., 1999 USA[211] | 11 healthy individuals (34±3) | ➢ >60 min supine rest<br>➢ 15 min standing upright | ➢ Hct<br>➢ Platelet count<br>➢ Platelet aggregation | ➢ Hct ↑ 3.3%<br>➢ Mean platelet aggregation ↑ 150±69%<br>➢ Platelet count ↑ from 197±10 to 229±9<br>➢ Yohimbine ($\alpha_2$-receptor blocker) inhibited the ↑ in platelet aggregation upon assuming the upright posture |
| Brown et al., 1999 UK[212] | 12 healthy volunteers (20-67) vs. 14 patients with orthostatic intolerance (24-64) | ➢ 20 min supine rest<br>➢ 20 min HUT ($60^0$)<br>➢ Participants completed protocol twice; one using impedance plethysmography to determine fluid | ➢ Calf segment change (Blood volume change)<br>➢ PVol (EB dye) | ➢ Greatest changes in calf segment change occurred within 1 min<br>➢ Rate of volume change between 4 – 10 min was significantly greater in patients compared to controls (14.22±1.43 vs. 8.41±1.02, respectively) |

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| | | shifts and the other using Evans blue dye dilution technique | | |
| Andrews et al., 1996 USA[213] | 17 healthy individuals (33±3) | ➢ Over night supine rest<br>➢ Stood upright for 26±4 min | ➢ Hct<br>➢ Platelet count<br>➢ Fibrinogen<br>➢ $F_{1+2}$<br>➢ Platelet aggregation<br>➢ t-PA antigen<br>➢ PAI-1 antigen<br>➢ Flow cytometry studies – (i.e. vWF, thrombin, GPIV, activated GPIIbIIIa, fibrinogen, P-sel) | ➢ Hct ↑ 7±1% (relative)<br>➢ Platelet count↑15±3%<br>➢ No change in plasma levels of fibrinogen when ΔHct was taken into account<br>➢ $F_{1=2}$ ↑ 22±6% which remained significant after ΔHct was taken into account<br>➢ t-PA antigen level ↑ 25±7% which remained significant after ΔHct was taken into account<br>➢ No change in plasma levels of PAI-1 antigen<br>➢ Significant ↑ in platelet aggregation (ADP and collagen)<br>➢ No change in any of the markers assessed by flow cytometric analysis |
| Gebara et al.,1996 USA[214] | 13 patients with mild to moderate hypertension (45±9) | ➢ Placebo controlled cross-over trial: Patients randomised to either placebo or verapamil for 4 week prior to each of the sessions<br>➢ 45 min supine rest<br>➢ 45 min standing upright | ➢ vWF<br>➢ t-PA antigen<br>➢ PAI-1 antigen<br>➢ Platelet aggregation | ➢ Platelet aggregation ↑ significantly during the placebo session but not during the verapamil session<br>➢ No change in t-PA, PAI-1 and vWF antigen |
| Bjerkhoel et al., 1995 Sweden[215] | 7 healthy males (24-35) | ➢ ≥60 min supine rest<br>➢ 15 min HUT ($85^0$)<br>➢ Measurements taken from arterial and venous blood at end of supine rest, at the end of 15 min HUT, and frequently throughout the supine recovery | ➢ Hct<br>➢ PVol (radio-labelled albumin)<br>➢ Δ PVol (HctHb method) | ➢ 7.5% ↑ Hct (relative) from arterial blood at end of tilt, which ↑ 10% within 90 seconds after being returned to supine<br>➢ 16.9% ↓ PVol (638 mL)<br>➢ 10.1 ↑ Hct (relative) from venous blood |
| Gleerup et al., 1995 Denmark[216] | 12 borderline hypertensive patients (58.8; 50-65) vs. 12 healthy individuals (62.8; 51-70) | ➢ 30 min supine rest<br>➢ 10 min standing upright | ➢ ECLT<br>➢ PAI-1 antigen<br>➢ t-PA antigen<br>➢ Platelet aggregation<br>➢ B-TG<br>➢ PF-4 | ➢ ELCT ↓ in both groups to a similar degree<br>➢ t-PA ↑ in both groups to a similar degree<br>➢ B-TG ↑ in the hypertensive group<br>➢ Platelet aggregation, PF-4, and PAI-1 demonstrated no change |
| Hinghofer et al., 1995 USA[217] | 8 healthy male individual (18-26) | ➢ 45 min supine rest<br>➢ 45 min HUT ($70^0$) followed by a 45 min supine rest, and a second 45 min HUT ($70^0$)<br>➢ Examined the effect of fluid ingestion (hypotonic, and isotonic) on PVol shifts | ➢ Hct<br>➢ PVol (Mass densitometry apparatus) | ➢ Hct ↑ 4% following the first HUT and 3% following the second HUT<br>➢ PVol ↓ by between 9.7 – 16.7%<br>➢ Fluid ingestion failed to attenuate the posture induced hemoconcentration |
| Patterson et al.,1995 USA[218] | 40 healthy individuals (30.05±7.36) | ➢ 30 min seated rest<br>➢ 10 min standing upright | ➢ Δ PVol (Hct/Hb method) | ➢ PVol ↓ |
| Lundvall et al.,1994 Sweden[219] | 10 healthy male individuals (28;24-38) | ➢ 60 min supine rest<br>➢ 15 min HUT ($85^0$)<br>➢ Measurements obtained from both arterial and | ➢ PVol (radio-labelled albumin) | ➢ Atrerial blood samples significantly underestimated the loss of PVol during the HUT<br>➢ PVol ↓ 336 mL at the end of the tilt |

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| | | venous circulation<br>➢ Samples obtained at end of rest, at min 5, 10, and 15 during the tilt, and frequently throughout the recovery | | ➢ Samples obtained 1 min after being returned to the supine position demonstrated a PVol loss of 511 mL |
| Muldoon et al.,1992<br>USA[220] | 26 healthy male individuals (18-30) | ➢ Unspecified period of supine rest<br>➢ 20 min standing upright | ➢ Hct | ➢ Hct ↑ approx. 3.7% |
| Geers et al., 1986<br>Netherlands[221] | 12 patients with nephrotic syndrome (23; 14-33) vs. 12 healthy individuals (22.8; 21-28) | ➢ 120 min supine rest<br>➢ 110 min standing upright<br>➢ Measurements taken prior to standing, and at 10, 25, 45, and 110 min during task | ➢ Hct (microhaematocrit)<br>➢ Δ PVol (Hct/Hb method) | ➢ Hct ↑ 4.6% and 3.3% in the patients and controls, respectively<br>➢ PVol ↓ 471 mL (16.3% ) and 347 mL (11.7% ) in patients and controls, respectively<br>➢ PVol ↓ was maximum at 25 min |
| Hinghofer et al.,1986<br>USA[222] | 13 healthy individuals (19-30) | ➢ 45 min supine rest<br>➢ 45 min HUT ($70^0$) followed by a 45 min supine rest, 45 min HUT ($70^0$), and a further 45 min supine rest | ➢ Δ PVol (Mass densitometry apparatus) | ➢ PVol ↓ 14% |
| Vargas et al.,1982<br>UK[223] | 9 healthy young (31$\pm$3.2) vs. 8 healthy old individuals (71$\pm$5.1) | ➢ 20 min supine rest<br>➢ 10 min HUT ($70^0$) | ➢ Δ PVol (Hct/Hb method) | ➢ PVol ↓ 12.4%<br>➢ No difference between groups |
| Tarazi et al., 1970<br>USA[224] | 12 healthy individuals vs. 21 hypertensive individuals | ➢ 35 – 45 min supine rest<br>➢ 20 min HUT ($50^0$) | ➢ Δ PVol | ➢ Hypertensive and healthy individuals demonstrated a similar reduction in PVol during the tilt test |
| Nielson et al., 1968<br>Denmark[225] | 21 healthy males vs. 11 healthy females (18-58) | ➢ 40 min supine rest<br>➢ Stood upright for 40 min | ➢ Δ PVol (Colloid osmotic pressure) | ➢ PVol ↓ 16% (maximum change) |
| Eisenberg et al., 1965<br>USA[226] | 7 normotensive vs.14 essential hypertensive individuals (40 – 68) | ➢ Unspecified baseline period<br>➢ 20 min motionless standing | ➢ Hct<br>➢ Δ PVol | ➢ Hypertensive individuals demonstrated a significantly greater ↓ in PVol (7.3% vs. 13.2%, respectively) and ↑ in Hct compared to the healthy individuals |
| Sloan et al., 1955<br>South Africa[227] | 13 healthy male individuals (19-22) | ➢ 25 min supine rest<br>➢ Stood upright for 10 min<br>➢ Measurements taken at min 1 and 10 | ➢ Platelet count | ➢ Significant ↓ in platelet count after 1 and 10 min |

β-TG = Beta Thromboglobulin, ECLT = Euglobulin Clot Lysis Time, F1+2 = Prothrombin Fragments 1+2, GP = Glycoprotein, Hct = Haematocrit, Hb, Haemoglobin, HUT = Head-up tilt, mL = Millilitres, Min = minutes, NS = Non significant, P-Sel = P-selectin, PVol = Plasma volume, t-PA = tissue-type Plasminogen activator, PAI -1 = Plasminogen Activator Inhibitor, PF-4 = Platelet Factor-4, vWF = von Willebrand Factor, ↑ = increased , ↓ = decreased, Δ = change, > = Greater, $\geq$ = Greater than or equal to,

Table 1.13: Summary of studies examining the haemostatic and platelet response to acute physical activity

| Author, year, place | Participants (Mean + SD age, years) | Study Design | Stress Task | Measurements | Results | Study limitation |
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| ***(a) Low Intensity Exercise*** | | | | | | |
| *Healthy Population Studies* | | | | | | |
| Szymanski et al., 1994 USA[237] | 14 healthy male sedentary participants (34.7 ± 4) vs. 12 regularly active participants (34.8 ± 4) | ➢ 2 visits: 1 visit in the morning and 1 visit in the evening<br>➢ 30 mins low intensity exercise | ➢ 50% $VO_2$Max | ➢ t-PA activity<br>➢ PAI-1 activity | ➢ Significant ↑ in t-PA activity with exercise; largest ↑ in the evening<br>➢ PAI-1 activity was significantly ↑in the inactive group compared to the active group<br>➢ PAI-1 activity was significantly ↑in the morning compared to the evening | ➢ No females included<br>➢ No recovery period |
| *Patient Population Studies* | | | | | | |
| Eriksson-Berg et al., 2002 Sweden[238] | 25 women with ACS (60; 54 – 67) vs. 25 healthy women (60; 55 – 67) | ➢ 1 visit<br>➢ 60 mins supine rest, followed by30 mins exercise | ➢ 50% $W_{max}$ on bicycle ergometer | ➢ Fibrinogen<br>➢ vWF antigen<br>➢ TAT<br>➢ D-dimer<br>➢ t-PA antigen and activity<br>➢ PAI-1 activity | ➢ ↑ levels of vWF, t-PA, PAI-1 in patients compared to controls<br>➢ Significant ↑ in fibrinogen, vWF, and t-PA antigen and activity following exercise in patients | ➢ No recovery period<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| ***(b) Moderate Intensity Exercise*** | | | | | | |
| *Healthy Participants* Studies | | | | | | |
| Ersoz et al., 2003 Turkey[239] | 12 healthy sedentary females (19 – 24) | ➢ 2 visits: 1 in late follicular and 1 in mid-luteal phase of menstrual cycle<br>➢ 15 mins of sub-maximal exercise | ➢ 70% $VO_2$Max on bicycle ergometer | ➢ Platelet count<br>➢ Platelet aggregation<br>➢ $TxB_2$ | ➢ Platelet count and platelet aggregation significantly ↑ following exercise. No difference between two phases of menstrual cycle<br>➢ $TxB_2$ levels were significantly ↑ in mid-luteal phase compared to late follicular phase<br>➢ $TxB_2$ significantly ↑ following exercise in the late follicular phase | ➢ No recovery period<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Ikarugi et al., 1999 Japan[240] | Male participants (19 – 34) | ➢ 1 visit<br>➢ 20 mins moderate intensity exercise | ➢ 60% $VO_2$Max on bicycle ergometer | ➢ Ex vivo shear stress induced haemostatic plug formation | ➢ Shear stress induced platelet reactivity significantly ↑ following exercise | ➢ No details on participant numbers<br>➢ No females included<br>➢ No recovery period |
| Todd et al., | 9 young males (27.8 ± | ➢ 1 visit | ➢ 70 – 75% | ➢ $TxB_2$ | ➢ Resting $TxB_2$ was significantly ↑in the | ➢ Small sample |

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| 1994<br>USA[241] | 0.8) vs. 9 older males (55.4 ± 1.3) | ➢ 15 mins rest, 30 mins exercise, followed by 30 mins recovery | $VO_2$Max on a treadmill | ➢ β-TG | older group<br>➢ No change in $TxB_2$ following exercise but significant ↑in older group at 30 mins recovery<br>➢ No change in β-TG in either group following exercise | ➢ No females included<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Dufaux et al., 1984<br>Germany[242] | Group A: 12 untrained elderly patients (60.6 ± 4.3) vs. Group B: professional soccer players (26.2 ± 3.7) vs. Group C moderately trained young subjects (23.3 ± 1.9) | ➢ 1 visit<br>➢ Moderate/high intensity exercise | ➢ Group A and B = maximal bicycle ergometer test; Group C = 45 mins sub-maximal bicycle ergometer test | ➢ FDP<br>➢ Fibrinogen | ➢ No significant change following exercise in any of the 3 groups | ➢ No females in two groups<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume<br>➢ Poorly defined and reported method and results |
| *Patient Population Studies* | | | | | | |
| Ivey et al., 2003<br>USA[243] | 18 stroke patients with hemiparetic gait deficits (66 ± 8) | ➢ 1 visit<br>➢ Rest, 20 mins exercise, followed by 60 mins recovery | ➢ Walking on treadmill at 60% maximal HR | ➢ t-PA activity<br>➢ PAI-1 activity | ➢ t-PA activity significantly ↑ following exercise.<br>➢ t-PA activity remained significantly elevated 60 mins post exercise<br>➢ PAI-1 activity significantly ↓ following exercise<br>➢ PAI-1 activity remained significantly depressed 60 mins post exercise | ➢ No control group |
| Morris et al., 2003<br>UK[244] | 10 obese sedentary individuals (43.3 ± 1.5) vs. 10 non-obese sedentary individuals (43.3 ± 1.9) | ➢ 1 visit<br>➢ 75 mins seated rest, 30 mins exercise, followed by 30 mins recovery | ➢ 70% $VO_2$Max on treadmill | ➢ PAI-1 antigen<br>➢ t-PA antigen | ➢ Obese individuals had significant ↑ in resting, exercise and post exercise levels of PAI-1 compared to non-obese<br>➢ t-PA significantly ↑ following exercise in the non-obese but showed no change in the obese group<br>➢ PAI-1 significantly ↑ in the post exercise recovery in obese group | ➢ No females<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Womack et al., 2001<br>USA[245] | 9 patients with PAD (70 ± 6) | ➢ 1 visit<br>➢ 30 mins rest, 30 exercise, followed by 60 mins recovery | ➢ Walking on a treadmill at 65% $VO_2$ Max | ➢ t-PA antigen and activity<br>➢ PAI-1 antigen and activity | ➢ t-PA activity significantly ↑ and PAI-1 activity significantly ↓ following exercise without changing t-PA and PAI-1 antigen levels, which remained into recovery | ➢ Small sample size<br>➢ No control group<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Desouza et al., 1997<br>USA[246] | 12 hypertensive males (69 ± 1) vs. 11 normotensive (65 ± 1) | ➢ 1 visit<br>➢ 15 mins seated rest followed by | ➢ 65% $VO_2$Max | ➢ t-PA antigen and activity<br>➢ PAI-1 antigen and | ➢ t-PA antigen and activity significantly ↑following exercise<br>➢ PAI-1 showed no change following | ➢ No females included |

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| | | 30 mins moderate intensity exercise | | activity | exercise<br>➢ No differences observed between groups | |
| ***(c) High Intensity Exercise and Incremental Exercise to Exhaustion*** | | | | | | |
| *Healthy Participants Studies* | | | | | | |
| Cooper et al., 2004 USA[247] | 8 healthy males (21.5 ± 1.5) | ➢ 1 visit<br>➢ 30 mins rest, strenuous exercise, followed by 10 mins recovery | ➢ $VO_2$ Max test | ➢ t-PA antigen and activity<br>➢ PAI activity | ➢ t-PA antigen and activity significantly ↑ during exercise task<br>➢ t-PA antigen and activity began to return to resting levels 4 mins post exercise<br>➢ PAI activity significantly ↓ following exercise but failed to return to return to resting levels within the 10 mins post-exercise recovery period | ➢ Small sample size<br>➢ Short recovery period<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Di Massimo et al., 2004 Italy[248] | 15 healthy sedentary males (25; 20 – 28) | ➢ 1 visit<br>➢ 60 mins rest, incremental exercise test, and 24 hrs recovery | ➢ 3 mins warm-up at 20 watts followed ↑ of 40 watts every 3 min until exhaustion on cycle ergometer | ➢ Platelet aggregation | ➢ ADP and collagen-induced platelet aggregation significantly ↑ following exercise and returned to resting levels after 24 hours recovery | ➢ No females included |
| Wang et al., 2004 Taiwan[249] | 18 healthy sedentary males (23.1 ± 0.8) | ➢ 1 visit<br>➢ 30 mins of rest followed by high intensity exercise | ➢ 80% $VO_2$ Max on bicycle ergometer for 40 mins | ➢ vWF antigen and activity<br>➢ Sheer stress induced platelet aggregation<br>➢ vWF binding to platelets<br>➢ GP IIb/IIIa expression<br>➢ P-sel expression | ➢ Significant ↑ in vWF antigen and activity following exercise<br>➢ Significant ↑ in shear stress induced platelet aggregation following exercise, accompanied by ↑ vWF binding, GP IIb/IIIa and P-sel expression | ➢ No females included<br>➢ No recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Cerneca et al., 1999 Italy[250] | Healthy males:<br>(1) 7 competition rowers vs. (2) 12 marathon runners vs. (3) 7 competition weightlifters vs. (4) 7 sedentary (not reported here) | ➢ 1 visit<br>➢ Strenuous exercise | ➢ Tested to near-maximal cardiovascular and muscular exertion | ➢ PT<br>➢ aPTT<br>➢ Fibrinogen<br>➢ Antithrombin III<br>➢ F1 + 2<br>➢ t-PA antigen<br>➢ PAI-1 activity | ➢ Group 1 demonstrated a significant ↑in fibrinogen, antithrombin III, F 1 + 2 and t-PA with a concomitant ↓in aPTT and PAI-1<br>➢ Group 2 demonstrated a significant ↑fibrinogen, antithrombin III and t-PA with a concomitant ↓aPTT and PAI-1<br>➢ Group 3 demonstrated no significant variation in variables | ➢ Small numbers in each group<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |
| Cuzzolin et al., 1999 Italy[251] | 12 healthy participant (6 inactive (21 ± 2.4) vs. 6 active (22.5 ± 2.1) | ➢ 1 visit<br>➢ Incremental exercise, steady state exercise, | ➢ Exercise on bicycle ergometer for 5 mins until reached 150 bpm | ➢ Platelet/neutrophil adhesion | ➢ Active participants demonstrated a significantly ↓in adhesion following exercise<br>➢ No change observed in the inactive | ➢ Small sample size<br>➢ No control for female menstrual cycle |

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| | | followed by 60 mins recovery | followed by 10 mins at same intensity | | group | |
| El-Sayad et al 1999 UK[252] | 8 moderately active males (26.6 ± 3.6) | ➢ 1 visit<br>➢ High intensity exercise followed by 30 mins recovery | ➢ Exercise on bicycle ergometer for 30 mins at 75% $VO_2$Max | ➢ Fibrinogen | ➢ When corrected for plasma volume, exercise induced a significant ↓in fibrinogen levels | ➢ Small sample size<br>➢ No females included |
| Mockel et al., 1999 Germany[253] | 13 amateur triathletes (25: 19 – 44) vs. 5 healthy male subjects (27 – 33) | ➢ 1 visit<br>➢ 30 mins supine rest, followed by strenuous exercise. Blood taken at rest, during aerobic and anaerobic exercise and during a 90 mins recovery | ➢ Exercise on cycle ergometer in supine position<br>➢ 30 mins aerobic exercise followed by an anaerobic period with a gradual ↑in load of 40 watts every 4 mins until exhaustion | ➢ P-sel<br>➢ F 1+2<br>➢ TAT<br>➢ PAP<br>➢ FM | ➢ P-sel expression significantly ↑following aerobic exercise and was more pronounced after anaerobic exercise<br>➢ P-sel expression returned to baseline level after 30 mins recovery<br>➢ F 1+2, FM, and PAP significantly ↑following aerobic exercise and was more pronounced after anaerobic exercise | ➢ No females included<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Ottersetter et al., 1999 USA[254] | 14 female oral contraceptive users (26.4 ± 1.1) vs. 14 non-users (26.7 ± 1.3) | ➢ 3 visit<br>➢ 15 mins seated rest followed by strenuous exercise | ➢ Maximal graded exercise test on bicycle ergometer | ➢ PAI-1 activity<br>➢ t-PA activity<br>➢ F 1+2 | ➢ t-PA significantly ↑ following exercise and although a trend was observed no significant difference was observed between groups<br>➢ PAI-1 significantly ↓ following exercise with the decrease being significantly greater in the non-user group<br>➢ $F_{1=2}$ were elevated at baseline in the oral contraceptive users but no change was observed in either group with exercise | ➢ No recovery period |
| Kvernmo et al., 1997 Norway[255] | 8 trained males (25 ± 0.9) vs. 8 non-trained males (20 ± 0.2) | ➢ 1 visit<br>➢ 10 mins warm up followed by 40 mins strenuous exercise | ➢ 80% $VO_2$Max | ➢ F 1+2<br>➢ TAT<br>➢ t-PA antigen<br>➢ PAI-1 antigen | ➢ F 1+2 significantly ↑in the non-trained group following exercise<br>➢ t-PA was significantly ↓at rest in the trained group<br>➢ ↑t-PA observed following exercise was significantly ↓ in the trained group compared to the non trained group<br>➢ PAI showed no significant change in response to exercise | ➢ Small sample size<br>➢ No females included<br>➢ Groups not age-matched<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Sakita et al., 1997 Japan[256] | 16 healthy males (22.6 ± 1.9) | ➢ 1 visit<br>➢ Incremental exercise task | ➢ Modified Bruce Protocol | ➢ Platelet aggregation<br>➢ Platelet sensitivity to SIN-1 | ➢ Collagen-induced platelet aggregation significantly ↑after vigorous exercise<br>➢ ↑ in platelet aggregation was | ➢ No females included |

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| | | | | ➢ Cyclic GMP accumulation inside the platelets | significantly ↓in the presence of SIN-1<br>➢ Cyclic GMP inside the platelets showed no significant change after exercise | |
| Gonzales et al., 1996 Spain[257] | 24 healthy sportsmen (20 – 27) vs. 23 healthy sedentary (22 – 28) vs. 11 healthy adult sportsmen (40 – 54) vs. 10 healthy sedentary adults (30 – 48) vs. 10 healthy elderly (60 – 80) | ➢ 1 visit<br>➢ Incremental strenuous exercise followed by 30 mins recovery | ➢ Bicycle incremental exercise starting at 50 watts ↑ by 50 watts every 10 mins until exhaustion | ➢ Platelet count<br>➢ β-TG | ➢ Platelet count significantly ↑ in the sedentary adults and sedentary elderly group following exercise<br>➢ β-TG at rest ↑ with age and is ↓in athletes compared to non-athletes<br>➢ β-TG significantly ↑following exercise in all groups | ➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Gleerup et al., 1995 Denmark[258] | 12 normotensive (62.8) vs. 12 borderline hypertensive (58.8) | ➢ 1 visit<br>➢ Supine rest, 10 mins standing, followed by 5 mins incremented exercise | ➢ 3 mins exercise at 50 watts for one min ↑by a 50 watts per min last 2 mins | ➢ Platelet aggregation<br>➢ β-TG<br>➢ PF-4<br>➢ ECLT<br>➢ t-PA activity<br>➢ PAI-1 | ➢ ECLT and PAI-1 were significantly ↑at baseline in the hypertensive group compared to the healthy controls<br>➢ ECLT was significantly ↓following exercise in both groups<br>➢ t-PA was significantly ↑following exercise in both groups<br>➢ Platelet aggregation, β-TG and PF-4 were unchanged by exercise in both groups | ➢ No recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| van den Burg et al., 1995 Netherlands[259] | 29 sedentary males (24.6 ± 0.6) | ➢ 1 visit<br>➢ 30 mins high intensity | ➢ 10 mins cycling with load ↑ until 70% $VO_2$Max was reached (A), 15 mins during which this work rate was maintained (B), stepwise ↑ in load until $VO_2$Max was achieved (C) followed by 10 mins active recovery and 15 mins passive recovery (D) | ➢ FVII:C<br>➢ FVIII:C<br>➢ FIX:C<br>➢ FXII:C<br>➢ Fibrinogen<br>➢ t-PA antigen and t-PA activity<br>➢ PT<br>➢ aPTT | ➢ Period A resulted in a significant ↑in all clotting factors and t-PA and a subsequent ↓in PT and aPTT<br>➢ Period B resulted in a significant ↑ in t-PA antigen and activity levels and a further ↑in FVIII:C and ↓in aPTT<br>➢ Period C resulted in all clotting factors, clotting times and fibrinolytic variables showing the most pronounced changes<br>➢ During recovery all clotting factors demonstrated a ↓ except FVIII:C which continued to ↑<br>➢ Correction for changes in PVol did not effect the results for FVIII:C, t-PA antigen and activity but reversed the outcome for FVII:C | ➢ No females included |
| Szymanski et al., 1994 USA[260] | 15 sedentary males (34.7 ± 4) vs. 15 active males (35.4 ± 4) vs. 15 highly active males (32.4 ± 3.6) | ➢ 1 visit<br>➢ 10 mins rest followed by an incremental exercise test | ➢ Modified Balke treadmill exercise protocol | ➢ t-PA activity<br>➢ PAI-1 activity | ➢ At rest t-PA activity was similar among all groups<br>➢ t-PA activity significantly ↑in all groups with exercise, although a greater response was observed in non-sedentary | |

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| | | | | | groups<br>➢ PAI-1 activity was significantly ↓in highly active group at rest compared to other groups<br>➢ PAI-1 significantly ↓in all groups following exercise | |
| Kestin et al., 1993<br>USA[261] | 12 physical active participants (39.3 ± 9.2) vs. 12 sedentary participants (37.9 ± 9.1) | ➢ 1 visit<br>➢ Blood taken immediately pre- and post-exercise and after 15 mins recovery | ➢ Bruce Protocol | ➢ GP1b (6D1)<br>➢ GPIIbIIIa (PAC-1)<br>➢ GPIV (OKM5)<br>➢ GMP-140 (S12) | ➢ Platelets from physically active and sedentary individuals at rest were comparable<br>➢ Exercise had no effect on the activation state of platelet in the physically active individuals<br>➢ Exercise yielded a significant alteration in platelet activation demonstrated by a significant ↑in antibody GPIb and OKM5 | |
| Gough et al., 1991<br>UK[262] | 7 healthy participants (25.6: 24.5 – 28) | ➢ 1 visit<br>➢ 10 mins rest followed by incremental exercise test | ➢ Bruce Protocol | ➢ ECLT<br>➢ t-PA antigen<br>➢ PAI-1 antigen and activity | ➢ ECLT, PAI antigen and activity were significantly ↓following exercise<br>➢ t-PA significantly ↑following exercise | ➢ Small sample size<br>➢ No recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Naesh et al., 1990<br>Denmark[263] | 8 healthy males (25: 22 – 29) | ➢ 1 visit<br>➢ 15 mins supine rest, incremental exercise followed by 60 mins supine recovery | ➢ Cycling on ergometer ↑workload by 50 watts every 5 mins until a HR of 150 bpm was reached and continued for 5 mins | ➢ Platelet count<br>➢ Platelet aggregation<br>➢ β-TG | ➢ Platelet count significantly ↑ following exercise and returned to baseline during recovery period<br>➢ β-TG demonstrated no change during exercise<br>➢ ADP-induced platelet aggregation significantly ↑ following exercise and remained elevated during recovery | ➢ Small sample size<br>➢ No females included<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| LaCroix et al., 1990<br>USA[264] | 20 healthy males (18 – 35) | ➢ 1 visit<br>➢ 5 mins rest in hyperbaric chamber followed by incremental exercise at 3 atmospheric absolutes | ➢ 1 mins cycling on ergometer at 60 rpm (unloaded) followed by 1 watt ↑per min in load until exhaustion | ➢ FVIII:C<br>➢ vWF antigen<br>➢ Plasminogen<br>➢ Antithrombin III | ➢ FVIII:C and vWF significantly ↑following exercise<br>➢ No differences observed between change elicited at 3 atmospheric absolutes compared to those at 1 atmospheric absolute | ➢ No females included<br>➢ No recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Vene et al., 1990<br>Yugoslavia[265] | 19 healthy males (24 ± 3) | ➢ 1 visits:<br>➢ Incremental exercise test | ➢ Bruce protocol | ➢ t-PA antigen<br>➢ PAI-1 antigen | ➢ t-PA significantly ↑following exercise<br>➢ PAI-1 demonstrated no change | ➢ No females included<br>➢ No recovery period<br>➢ Failed to correct alterations in |

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| Chen et al., 1989 Taiwan[266] | 51 young healthy participants females (23 ± 1); males (25 ± 1) | ➢ 1 visit<br>➢ High intensity exercise | ➢ Exercised on bicycle ergometer at ¾ of maximum work load | ➢ Bleeding time<br>➢ Platelet count | ➢ At rest females demonstrated significantly ↑bleeding times compared to males<br>➢ Bleeding time significantly ↓following exercise in both males and females<br>➢ Platelet count significantly ↑following exercise | ➢ No recovery period |
| Ferguson et al., 1987 USA[267] | 20 male marathoners (37.2 ± 1.9) vs. 20 male joggers (35.3 ± 1.9) vs. 20 male sedentary (33.9 ± 2.1) | ➢ 1 visit<br>➢ 10 mins rest, incremental exercise, followed by 30 mins recovery | ➢ Bruce protocol on treadmill | ➢ Platelet count<br>➢ FDP<br>➢ PT<br>➢ aPTT<br>➢ Antithrombin III<br>➢ ECLT | ➢ Platelet count, PT, aPTT significantly ↓following exercise in all three groups<br>➢ FDP significantly ↑in all groups except sedentary individuals<br>➢ Antithrombin III significantly ↑in all three groups<br>➢ ECLT significantly ↓following exercise | ➢ No females included<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Wheeler et al., 1986[268] | 19 healthy males (33 ± 1.8) | ➢ 1 visit<br>➢ 5 mins rest, incremental exercise test, followed by 8 mins recovery | ➢ Branching multistage treadmill protocol | ➢ FVIII:C antigen and activity<br>➢ FA | ➢ FA significantly ↑following exercise but did not ↓to resting levels in the 8 mins recovery<br>➢ FVIII:C antigen and activity significantly ↑following exercise and continued to ↑over the recovery period | ➢ No females included<br>➢ Short recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Mangum et al., 1984 USA[269] | 10 males participants (27.1 ± 2.5) | ➢ 1 visits<br>➢ 15 mins rest followed by incremental exercise | ➢ 50 watts for 5 mins and 150 watts for 10 mins | ➢ ECLT<br>➢ aPTT | ➢ ECLT significantly ↓ following exercise<br>➢ aPTT demonstrated no change | ➢ Small sample size<br>➢ No females included<br>➢ No recovery period |
| *Patient Population Studies* | | | | | | |
| Yilmaz et al., 2004 Turkey[270] | 63 male participants with positive exercise tests for CAD (52.4 ± 4.1) vs. 35 participants with non significant CAD on angiography (52.6 ± 4.3) | ➢ 1 visit<br>➢ Rest and an incremental exercise test | ➢ Modified Bruce Protocol | ➢ MPV | ➢ MPV ↑ significantly post exercise in CAD group but not in control group | ➢ No recovery period<br>➢ No females included<br>➢ Poorly detailed methodology and results |
| Gibbs et al., 2001 UK[271] | 20 CHF patients (64 ± 10) vs. 20 patients with vascular disease (63 ± 11) vs. 20 healthy controls (63 ± | ➢ 1 visit<br>➢ 20 mins rest, incremental exercise to exhaustion, | ➢ Modified Bruce Protocol | ➢ vWF antigen<br>➢ sP-Sel<br>➢ Fibrinogen | ➢ Significant ↑ in fibrinogen following exercise which remained elevated during recovery<br>➢ No change in vWF and sP-Sel for either group following exercise | ➢ No comparison to healthy controls reported<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume |

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| | 9) | followed by 30 mins recovery | | | | ➢ Failed to control for female menstrual cycle |
| Li-Saw-Hee et al., 2001 UK[272] | 20 patients with chronic AF (65 ± 11) 20 patients with vascular disease (63 ± 11) vs. 20 healthy controls (63 ± 9) | ➢ 1 visit<br>➢ Incremental exercise to exhaustion followed by 20 mins recovery | ➢ Bruce Protocol | ➢ Fibrinogen<br>➢ sP-sel<br>➢ vWF antigen<br>➢ PAI-1 antigen | ➢ Significant ↑ in fibrinogen in AF patients following exercise<br>➢ PAI-1 significantly ↓following exercise in AF patients<br>➢ No change in vWF and sP-sel | ➢ No comparison to healthy controls reported<br>➢ Failed to correct alterations in coagulatory markers for Δ in plasma volume<br>➢ Failed to control for female menstrual cycle |
| Lindemann et al., 1999 Germany[273] | 12 patients with CAD (61.7 ± 1.7) vs. 11 healthy controls (58 ± 2.5) | ➢ 1 visit<br>➢ 20 mins supine rest followed by incremental exercise test | ➢ Cycling on ergometer commencing at 50 watts and↑steadily by 25 W every 3 mins | ➢ P-sel expression<br>➢ Fibrinogen binding to GP IIb/IIIa and its expression | ➢ Resting fibrinogen binding to GP IIb/IIIa and P-sel expression was significantly ↓in patients and ↓further after exercise | ➢ Failed to control for female menstrual cycle<br>➢ No recovery period |
| Wang et al., 1999 Taiwan[274] | 15 sedentary males (24.3 ± 1.1) | ➢ 1 visit<br>➢ 30 mins rest, followed by strenuous exercise | ➢ $VO_2$Max test | ➢ Platelet adhesion | ➢ ADP-induced platelet adhesion was significantly ↑ following exercise | ➢ Small sample size |
| Mustonen et al., 1998 Finland[275] | 15 patients with PAD (59 ± 8) vs. healthy controls (57 ± 11) | ➢ 1 visit<br>➢ 15 mins rest, incremental exercise test, followed by 30 mins recovery | ➢ Exercise on a treadmill at constant speed of 3.2 km/h for 2 mins at $0^0$ thereafter the inclination angle was ↑by $2^0$/ 2 mins | ➢ vWF<br>➢ TAT<br>➢ D-dimer<br>➢ Fibrinogen<br>➢ t-PA antigen and activity<br>➢ PAI-1 antigen<br>➢ PAP | ➢ Fibrinogen, D-dimer, t-PA and PAI-1 antigen levels were ↑ in patient group<br>➢ Significant ↑ in TAT in patient group following exercise<br>➢ D-dimer, t-PA antigen and activity and PAP demonstrated a significant and parallel ↑in both patient and control groups | ➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume<br>➢ Failed to control for female menstrual cycle |
| Held et al., 1997 Sweden[276] | 809 stable angina patients (59 ± 7) vs. 50 healthy controls (61 ± 0.8) | ➢ 1 visit<br>➢ Incremental exercise test | ➢ Symptom limited exercise test on bicycle ergometer, starting at 30 watts with ↑in 10 watts per min | ➢ t-PA antigen and activity | ➢ t-PA antigen was significantly ↑in angina patients at rest compared to healthy controls<br>➢ t-PA antigen levels ↑following exercise with Δ being greatest in healthy individuals | ➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume<br>➢ No defined baseline or recovery period<br>➢ No control for female menstrual cycle |
| Hansen et al., 1994 Norway[277] | 14 patients with hypercholesterolaemia (49.7: 29 – 59) vs. 14 healthy participants | ➢ 1 visit<br>➢ 15 mins supine rest followed by strenuous | ➢ Cycling on ergometer starting at 75 watts and ↑by 25 | ➢ t-PA antigen and activity<br>➢ TAT<br>➢ Antithrombin III | ➢ t-PA was significantly ↑in patients at rest compared to health controls<br>➢ Both groups exhibited a similar and significant ↑in t-PA and TAT during | ➢ No recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |

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| | (49.6 ± 8.1) | exercise | watts every other mins up to 150 watts | activity | exercise<br>➢ ↑in t-PA activity was more pronounced in patient population | |
| Bounamaux et al., 1992 Switzerland[278] | 100 patients with confirmed or suspected CAD (55; 31 – 80) | ➢ 1 visit<br>➢ Incremental exercise | ➢ Diagnostic exercise test ≤ 80 APMHR | ➢ D-dimer<br>➢ TAT<br>➢ F 1+2 | ➢ TAT and F 1+2 significantly ↑following exercise<br>➢ D-dimer demonstrated no change following exercise | ➢ Blood not taken immediately after completion of exercise<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume<br>➢ No control for female menstrual cycle |
| Rydzewski et al., 1990 Japan[279] | Group 1: 23 healthy controls (55.2 ± 10.7)<br>Group 2: 23 patients with CAD without exercise induced schema (58 ± 10.4)<br>Group 3: 22 patients with CAD with transient exercise induced schema (56.8 ± 9.7) | ➢ 1 visit<br>➢ Incremental exercise test | ➢ Symptom limited exercise test on bicycle ergometer, starting at 50 watts ↑in 25 watts every 3 min | ➢ t-PA antigen<br>➢ PAI-1 antigen<br>➢ Plasminogen activator activity<br>➢ t-PA-PAI-1 complex | ➢ Patients in group 3 had significantly ↑resting levels of t-PA compared to the other two groups and ↑PAI-1 compared to group 1<br>➢ Exercise induced significant ↑in levels of t-PA, plasminogen activator activity, and activator inhibitor complex and a significant ↓PAI-1 | ➢ No recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| McGill et al., 1989 Australia[280] | 27 males CAD patients either asymptomatic or with chronic stable angina | ➢ 2 visits<br>➢ 30 mins supine rest followed by incremental exercise test same protocol on both visits | ➢ Bruce Protocol | ➢ $TxB_2$<br>➢ β-TG<br>➢ Platelet count | ➢ At rest $TxB_2$ were comparable between patients with positive and negative exercise tests and demonstrated no significant ↑with exercise<br>➢ Both groups of patients demonstrated a significant ↑in β-TG following exercise | ➢ No females included<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Martos et al., 1988 Hungary[281] | 17 male post–MI (2 months) patients (56.4 ± 4.8) | ➢ 1 visit<br>➢ Strenuous exercise | ➢ 85% of APMHR on bicycle ergometer | ➢ Platelet count<br>➢ Platelet aggregation | ➢ Neither platelet count or ADP-induced platelet aggregation changed during exercise | ➢ Small sample size<br>➢ No control group<br>➢ No females included<br>➢ No recovery period |
| Speiser et al., 1988 Germany[282] | Group A: 18 healthy athletes (23 ± 3.5)<br>Group B: 18 healthy sedentary participants (25.7 ± 2.7)<br>Group C: 17 elderly healthy volunteers (50.6 ± 7.7)<br>Group D: 18 patients with previous MI | ➢ 1 visit<br>➢ Incremental exercise test. Blood taken with patient in recumbent position prior to exercise and 2 and 60 mins post exercise | ➢ Group A & B started with a workload of 1 watt per kg body weight for 2 mins, ↑by 1 watt per kg every 2 mins<br>➢ Groups C & D started with a | ➢ D-dimer<br>➢ Fibrinogen<br>➢ t-PA antigen<br>➢ PAI-1 activity<br>➢ ECLT<br>➢ vWF | ➢ Groups C and D had significantly ↑resting levels of t-PA compared to groups A and B<br>➢ Group A exhibited significantly lower t-PA compared to Group B<br>➢ Groups B and D had significantly ↑PAI at rest<br>➢ ELT was prolonged in groups B and D<br>➢ t-PA significantly ↑in all groups during exercise with no differences being | ➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume<br>➢ Failed to account for female menstrual cycle |

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| | (54.2 ± 7.9) | | workload of 25 W/kg for 2 mins, ↑by 25 W/kg every 2 mins | | observed between groups<br>➢ ELT was significantly ↓in all groups following exercise, with ELT being shorter in groups A and C<br>➢ vWF significantly ↑in all groups but D immediately following exercise<br>➢ D-dimer and fibrinogen showed no significant change during exercise | |
| Strauss et al., 1985 USA[283] | 24 males with known CAD (60: 36 – 69) vs. 9 healthy / hypertensive male participants (40: 21 – 61) | ➢ 1 visit<br>➢ Incremental exercise test with blood taken immediately 5 and mins post exercise | ➢ Symptom-limited maximal exercise tolerance test on treadmill<br>➢ Standard or Sheffield-modified Bruce Protocol or Naughton protocol | ➢ PF-4<br>➢ β-TG | ➢ β-TG showed significant difference between the two groups at rest and during exercise<br>➢ PF-4 demonstrated a significant ↑during exercise in the control group but not in the patients with CAD | ➢ No females included<br>➢ No recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume<br>➢ Inadequate control group; not age-matched |
| Levine et al., 1984 USA[284] | 84 males patients (56.9; 31 – 70) scheduled for diagnostic treadmill exercise | ➢ 1 visit<br>➢ Exercise test | ➢ 63 patients and 10 healthy controls underwent a modified Bruce protocol<br>➢ 21 patients were studied at 2, 6, or 12 weeks following an MI using a symptom limited Naughton Protocol | ➢ Platelet count<br>➢ PF-4 | ➢ PF-4 was not significantly ↑during exercise in healthy participants<br>➢ PF-4 was significantly ↑following exercise in the post MI patients who underwent Naughton protocol | ➢ No females included<br>➢ No recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Rotmensch et al., 1983 USA[285] | 26 patients undergoing evaluation of CAD<br>Group A: exercise test only (50 ± 16<br>Group B: post exercise thallium scan (49 ± 10) | ➢ 1 visit<br>➢ Incremental exercise test with blood taken prior, immediately after, and 30 mins after completion of exercise | ➢ Incremental exercise test on treadmill | ➢ PF-4<br>➢ $TxB_2$ | ➢ Patient's in group A who experienced a positive exercise test demonstrated a significant ↑in PF-4, whereas patients whose exercise test was negative showed no change<br>➢ Patients in group B demonstrated significantly ↑resting PF-4 and a significantly greater ↑during in PF-4 compared to group A<br>➢ $TxB_2$ demonstrated no significant change with exercise | ➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume<br>➢ Insufficient demographic details on patients |
| Marcella et al., 1983 | 13 males with CAD (55: 36 – 69) vs. 10 | ➢ 1 visit<br>➢ Incremental | ➢ Incremental exercise test on | ➢ PF-4<br>➢ β-TG | ➢ PF-4 was significantly ↑in patient group at rest compared to healthy | ➢ No females included<br>➢ No recovery period |

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| USA[286] | healthy males (29:22 – 46) | exercise test | bicycle ergometer | ➢ $TxB_2$<br>➢ Fibrinopeptide A<br>➢ Fibrinopeptide B | participants but as with $TxB_2$, demonstrated no change during exercise<br>➢ Fibrinopeptide A was significantly ↑in patient group at rest but demonstrated no change with exercise<br>➢ Fibrinopeptide B demonstrated no change with exercise | ➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume<br>➢ Two groups not age- matched |
| Schernthaner et al., 1983 Austria[287] | 53 male post-MI (40 days to 2 years) patients (52) vs. 9 healthy males (47) | ➢ 1 visit<br>➢ Incremental exercise followed by 30 mins recovery | ➢ Symptom limited bicycle ergometer test | ➢ PF-4<br>➢ β-TG | ➢ At rest PF-4 and β-TG were significantly ↑in patients compared to controls<br>➢ PF-4 and β-TG significantly ↑following exercise in the healthy individuals but not in the patient group<br>➢ PF-4 and β-TG only significantly ↑in patients who achieved >75% of their predicted maximal work rate | ➢ No females included<br>➢ Groups were not age-matched<br>➢ Heterogeneity of MI patients<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Kopitsky et al., 1983 USA[288] | 20 healthy males (35 – 59) | ➢ 1 visit<br>➢ 15 mins rest followed by incremental exercise test | ➢ Modified Balke protocol on a treadmill | ➢ FVIII:C antigen<br>➢ Thrombin induced FVIII:C activity | ➢ FVIII:C antigen significantly ↑following exercise<br>➢ Thrombin induced a significant ↑ in FVIII:C at rest and post exercise<br>➢ ↑in FVIII probably due to activation of FVIII/vWF complex | ➢ No females included<br>➢ Blood samples not taken immediately after exercise<br>➢ No recovery period<br>➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Ek et al., 1982 Sweden[289] | 30 patients with MI (63; 50 – 78) vs. 26 healthy participants (66; 50 – 80) | ➢ 1 visit<br>➢ 10 mins rest followed by incremental exercise | ➢ Exercise on bicycle ergometer ↑10 W/min until pulse reached 150 bpm or until patient was unable to continue | ➢ PF-4 | ➢ PF-4 at rest was similar between controls and patients<br>➢ PF-4 was not significantly ↑following exercise in patient group | ➢ Failed to correct alterations in haemostatic markers for Δ in plasma volume |
| Khanna et al., 1975 India[290] | 20 males IHD (43.5; 26 – 52) vs. 8 healthy males (43; 25 – 53) | ➢ 1 visit<br>➢ 60 mins rest followed by incremental exercise | ➢ Modified Bruce protocol | ➢ ECLT | ➢ Fibrinolytic response to exercise was significantly greater in the control group compared to the patient group | ➢ No recovery period<br>➢ No females included |

ACS = Acute Coronary Syndromes, ADP = Adenosine Diphospate, AF = Atrial Fibrillation, APMHR = Age Predicted Maximal Heart Rate, bpm = beats per minute, β-TG = Beta Thromboglobulin, CAD = Coronary Artery Disease, CHF = Chronic Heart Failure, ECLT = Euglobulin Clot Lysis Time, F1+2 = Prothrombin Fragments 1+2, FVII:C = Clotting Factor VII, FVIII:C = Clotting Factor VIII, FIX:C = Clotting Factor IX, FXII:C = Clotting Factor XII, FA = Fibrinolytic Activity, FDP = Fibrin Degradation Products, GPIIb/IIIa = Glycoprotein IIb/IIIa, HR = Heart Rate, IHD = Ischemic Heart Disease, MPV = Mean Platelet Volume, mins = minutes, MI

= Myocardial Infarction, P-sel = P-Selectin, PAD = Peripheral Artery Disease, PAP = Plasmin α2 antiplasmin complex, t-PA = tissue-type Plasminogen activator, PAI -1 = Plasminogen Activator inhibitor, PF-4 = Platelet Factor-4, aPTT = activated Partial Thromboplatin Time , PT = Prothrombin Time, TAT = Thrombin-Antithrombin, TM = Thrombomodulin, $TxB_2$ = Thromboxane $B_2$, W = Watts, vWF = von Willebrand Factor, ↑ = increased , ↓ = decreased, Δ = change

# CHAPTER 2

# Methods

## 2.1 Questionnaire Study

### 2.1.1 Participants

Between the 25th November 2003 and 28th August 2005 all patients with a diagnosis of AF attending the specialist AF cardiology clinic at City Hospital, Birmingham, West Midlands, were eligible for inclusion. The presence of AF was defined as the absence of a P-wave in association with rapid oscillations or fibrillatory waves on a 12-lead ECG, by a physician. Patients were excluded from participation if they (1) were aged less than 18 years, (2) had undergone any non-pharmacological intervention (excluding DC cardioversion) to correct this arrhythmia, (3) had carcinoma/malignancy of any type, (4) had a myocardial infarction (MI) or transient ischemic attack (TIA)/stroke within the previous six months, (5) had coronary artery bypass graft (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA/PCI) within the previous six months, (6) could not read English, or (7) were cognitively impaired.

AF patients were age-, and sex-matched with a hypertensive disease control group. Between the 3rd January 2005 and 7th October, the notes of 215 hypertensive patients were screened and subsequent approaches were made to the 160 patients who were deemed eligible. The exclusion criteria for the hypertensive patients were identical to those employed for the AF patients.

During the study period, 195 AF and 156 hypertensive patients were approached to participate. Of these, 95 (48.7%) AF and 63 (39.4%) hypertensive patients refused to

participate. Consequently, 101 AF patients and 97 hypertensive patients provided written informed consent, completed the baseline questionnaires, and constitute the effective study population.

### 2.1.2 Procedure

Prior to each AF clinic, patient's notes were screened to identify potential participants for the study. Social and demographic details such as age, gender, ethnicity, and employment status were recorded. Patients deemed eligible were either approached following their clinic appointment and given a study information sheet, or invited by letter in the week following their clinic appointment. If the patient agreed to participate, written informed consent was obtained. The study protocol was reviewed and granted ethical approval by the West Birmingham Local Research Ethics Committee prior to commencement of the study.

Patients who participated in the study completed a battery of questionnaires on two separate occasions: at baseline, and at six-months. The questionnaire pack comprised the following: the Beck Depression Inventory (BDI) [291], the Stait-Trait Inventory (STAI) [292], and the Dartmouth Care Cooperative Information Project (COOP) chart system [293]. All questionnaires employed had acceptable psychometric properties. Patients completed the questionnaires either at home or in the Cardiovascular Psychophysiology Unit at the University Department of Medicine at City Hospital. If they expressed a preference to complete the battery of questionnaires at home, the questionnaire pack along with detailed instructions, consent forms (if not previously signed) and a stamped addressed envelope were sent to them. If the patient expressed

a preference to complete the questionnaire pack at hospital, this was done in the presence of an interviewer (GT).

#### 2.1.2.1 Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI) is a 21-item self-report inventory used to measure depressive symptoms in adolescents and adults [291]. The original BDI was derived from the clinical observation of attitudes and symptoms frequently displayed by depressed psychiatric patients, and infrequently by non-depressed psychiatric patients [291]. The clinical observations were then systematically combined, and constitute the 21-items on the inventory, measuring an individual's current depressive state. Each item describes specific behavioural manifestations of depression in a series of four or five self-evaluative statements. The statements are scored from zero to three, reflecting the severity of the symptom. The patient must circle the statement which best describes their current feelings. Scores range form zero to 63, with higher scores indicating greater levels of depressive symptoms. Scores between zero and nine are classified as non-depressed, scores 10 and 15 as mildly depressed, scores 16 to 23 as moderately depressed, and scores of 24 and over are classified as severely depressed [7]. A cut-off of 10 or greater was adopted in the present study to indicate depression; this criteria has been commonly employed previously in studies examining depression in patients with coronary heart disease (CHD) [295-297].

The BDI has been shown to have acceptable internal consistency with Cronbach's alpha coefficient of 0.86 for psychiatric patients and 0.81 for non-psychiatric patients. Variable test-retest reliability has been found with Pearson product moment correlations coefficients ranging from 0.48 to 0.86 for psychiatric patients and 0.60 to 0.83 for non-psychiatric individuals [298]. However, the BDI is a measure of current

depressive state and is therefore subjective to fluctuation over time, which may explain the occasional low test-retest reliability.

The concurrent validity of the BDI has been determined by comparing the reported scores with experts' clinical ratings of depression. Correlations between the two have ranged from 0.55 to 0.96 for psychiatric patients and 0.55 to 0.73 for non-psychiatric individuals [298]. The BDI has been widely used to assess depressive symptoms in medically-ill patients [299-300], and patients with heart disease [295-297,301-302]. Other well established instruments used to measure depression, such as the Hamilton Rating Scale for Depression [303] and the Zung Self-Rating Depression Scale [304] have been found to be strongly associated with the BDI.

#### 2.1.2.2 State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (STAI) is the most widely used instrument for measuring anxiety in adults [292]. It has been used extensively in research and clinical practice over the last 40 years to assess anxiety in medically-ill patients [305-306], and patients with heart disease [295,301,307]. The STAI compromises two separate self-report scales, consisting of twenty statements. The state anxiety scale evaluates how the respondents feel "right now", with the trait anxiety scale assessing how people "generally feel". Each STAI score is given a weighted score of one to four. A rating of four indicates the presence of a high level of anxiety for ten statements on the state anxiety scale and eleven statements on the trait anxiety scale. Conversely, a high rating indicates the absence of anxiety for the remaining ten state anxiety statements and nine anxiety items, and the scoring weights for these items are reversed. The state anxiety scale requires examinees to circle the number which best describes the intensities of their current feelings: (1) not at all, (2) somewhat, (3)

moderately so, and (4) very much so. Similarly, the trait anxiety scale asks people to indicate how they generally feel by rating the frequency of their feelings: (1) almost never, (2) sometimes, (3) often, and (4) almost always. Scores on both state and trait anxiety scales can range from a minimum of 20 to a maximum of 80, with higher scores indicating greater levels of anxiety. A full score may still be obtained for respondents who omit one or two items on either scale by determining the mean weighted score for the completed statements; multiplying this value by 20, and then rounding this figure to the nearest whole number. The STAI has been shown to have acceptable internal consistency across populations, with Cronbach's alpha coefficient of 0.93 and 0.91 for the State and Trait Anxiety scale, respectively.

#### 2.1.2.3 Dartmouth Care Cooperative Information Project (COOP) Charts

The Dartmouth Care Cooperative Information Project (COOP) chart system has been developed and refined over a decade for the purpose of making a brief, practical, and valid method to assess functional status of adults and adolescents [293]. Each chart comprises a question referring to the status of the patient over the last 4 weeks, each with five response choices. Each response is illustrated by a drawing that depicts a level of functioning or well-being, which are scored along a 5-point ordinal scale, with the higher scores representing unfavourable levels of health-related quality of life. The total score for the charts is 45; however, for the purposes of all subsequent analyses the score for the overall quality of life was not included in the total score. Therefore, the maximum total score was 40. The Dartmouth COOP charts have been used previously to assess functional status in both medically ill [308-309], and cardiac patients [296,310-311].

#### 2.1.2.4 Socio-economic status

Townsend deprivation scores were used as a measure of socio-economic status, and were allocated based on an individual's postal code [312]. Deprivation scores are composites of the extent of household overcrowding, unemployment, and lack of car and home ownership in small postal code areas across Britain. Scores range from -7.3 to 10.2, with higher positive scores indicating greater deprivation.

#### 2.1.2.5 Clinical variables

Baseline clinical characteristics, such as type of AF, date of diagnosis and duration of AF, whether or not the patient had undergone direct current (DC) cardioversion, whether they received a medication regimen for rate or rhythm control, and the presence of any other significant cardiovascular (i.e. hypertension, diabetes, coronary artery disease), and non-cardiovascular co-morbidities were documented from patients hospital notes.

#### 2.1.2.6 Medication

Prescriptions of anti-coagulant/anti-platelet medication (i.e. warfarin, aspirin, clopidogrel), digoxin, alpha- and beta-blockers, calcium channel blockers, diuretics, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers, spirolactone, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ('statins') were recorded from patient's records.

#### *2.1.2.10 Follow-up*

Patients enrolled in the study were followed up at six-months. Identical questionnaire packs to those completed at baseline were sent to patients together with a stamped

addressed envelope in which to return the second questionnaire pack. Outcome data, including the number of hospitalisations for cardiovascular events and/or death from any cause during the six-month follow-up period were recorded from the Patient Information System (PiMS) at the hospital.

## 2.2 Stress testing study

### 2.2.1 Participants

Of the 198 patients (101 AF and 97 hypertensive) who were enrolled in the questionnaire study (see section 2.2.1), 120 were not eligible for the stress testing component of the study for the following reasons: female (n=71), diabetes mellitus (n=41), heart failure (n=2), and anyone aged >80 years (n=96). Of the 78 eligible patients, 14 (17.9%) AF patients consented to take part in the stress-testing study. These patients were age-matched with 10 hypertensive patients and 10 healthy controls. Healthy individuals were required to undergo a thorough cardiovascular screening (echo-cardiography, ECG, full haemostatic profile) prior to giving informed consent.

### 2.2.2 Procedure

Patients attended the Cardiovascular Psychophysiology Unit, City Hospital NHS Trust, Birmingham on four separate occasions, two in a euhydrated state and two in a hyperhydrated state, the order of which was counterbalanced to prevent order effects. On arrival at the laboratory the protocol was described and patients provided written informed consent. Each patient then completed the food diary describing what food and drink they had consumed over the previous 24-hour period. Demographic characteristics, current medication, and medical co-morbidity were verified against details from patient's hospital records. Each patient was then asked to lay supine on

the tilt table (Model 501, Plinth 2000, UK). While in this position the body impedance analysis (BIA) was performed, the ECG and blood pressure (BP) cuff attached, and the cannula inserted. Following instrumentation and instruction (approximately 30-minute), participants' lay supine on the tilt table with their head supported for a period of 20-minutes. During this baseline period BP measurements were obtained at after 13, 15, 17 and 19 minutes, with blood being drawn upon completion. The patient then performed either the 12-minute mental or postural stress task, during which BP measurements were also obtained at minutes 5, 7, 9, and 11, with blood being drawn immediately upon completion. This was followed by a 60-minute recovery period in a supine position with BP measurements being taken at minutes 23, 25, 27, and 29, and minutes 53, 55, 57, and 59, with blood being drawn at 30 and 60 minutes (see Figure 2.1).

#### 2.2.2.1 Hydration manipulation

Patients completed testing sessions in one of two hydration states, euhydrated and hyperhydrated. For the euhydration manipulation, patients were given one 500 ml bottle of still water and instructed to consume the fluid in the 12-hour period prior to arrival at the laboratory. For example, if the testing session commenced at 9:00 a.m the participants were instructed to consume 250 ml after 9:00 p.m on the evening prior to testing and the remaining 250 ml within the hour prior to the commencement of testing in the morning. For the hyperhydrated manipulation, patients were given two 500 ml bottles contain water mixed with 50 mmol of $Na^+$ (sodium citrate, Tribasic: Dihydrate, Sigma®) and one sodium saccharin tablet, and instructed to consume the fluid in the 12-hour period prior to arrival at the laboratory. For both hydration manipulations, patients were instructed not to consume any food or other

drinks in the 12-hour period prior to arrival at the laboratory, in addition to withholding an prescribed medication. A dietary recall questionnaire was employed at the beginning each of the testing sessions to monitor food and fluid intake from the previous day and participants were asked to try and duplicate this as close as possible for each of the following testing sessions.

#### 2.2.2.2 Mental arithmetic stress task

The participants were required to complete an eight minute version of the paced auditory serial addition test (PASAT) in the supine position [313]. This task involves adding two sequentially presented single digit (1 – 9) numbers, while retaining the latter of the two numbers in their memory for subsequent addition to the next number presented. The task consisted of four two-minute periods with numbers being presented by a tape player (Sony, EFS-E14L) at rates of 4.0, 3.5, 3.0, and 2.5 seconds, respectively. Prior to administration of the PASAT, the task was explained and the patient was given a brief practice, which consisted of the presentation of 10 numbers. Patients were told to call the answer out loud, and if performance broke down, to continue by adding the next two sequentially presented numbers. The patients were also informed that their performance was being monitored and a loud noise burst would be delivered if they answered incorrectly or failed to respond. The PASAT has been widely used as a laboratory stress task and has been shown to evoke significant cardiovascular, rheological, and haemostatic changes [314-317].

#### 2.2.2.3 Postural stress task

In the postural stress task, each participant was tilted head-up (64°), strapped to a tilt table for 12 minutes. This position was chosen because it elicits 90% of the

cardiovascular response while avoiding the discomfort associated with standing upright on a tilt table [39]. A tilt of 12 minutes was chosen as it has been shown previously to elicit significant cardiovascular and rheological responses [315,319-320].

#### 2.2.2.4 Cardiovascular measures

Systemic blood pressure (systolic (SBP), diastolic (DBP), and mean arterial blood pressure (MAP)) and heart rate (HR) were measured from the left arm (unless contraindicated) using an automated auscultatory sphygmomanometer (Critikon, Dinamap). The first of the series of BP measurements was initiated manually, with subsequent measures being initiated automatically every other minute. Three dot ECG electrodes (Red Dot, 3M, Germany) were attached, two on the collar bone and one on a rib, to monitor the electrical activity of the heart.

#### 2.2.2.5 Body Impedance Analysis (BIA)

Total body water (TBW), intracellular water (ICW) and extracellular water (ECW) were determined using a Bioelectrical Body Composition (BIA) Analyzer (Quantum X, RJL Systems, USA) with the participant lying supine on the tilt table [321]. Sites were exfoliated and cleaned (Mediswab) before tab electrodes (Q-Trace Gold 5500, Kendall, USA) were placed on the right side of the body. The two signal electrodes were placed on the proximal phalanx of the middle finger and on the base of the second toe. The two detecting electrodes were placed on imaginary lines bisecting the ulnar head and the mallealus. Each participant's fluid composition was obtained by inputting reactance and resistance into the Cyprus 1.2 program (RJL systems, USA).

#### 2.2.2.6 Blood measures

##### 2.2.2.6.1 Blood sampling

The participant's right arm was inspected for a suitable anticubital vein, and if unsuitable for cannulation, their left arm was inspected. Venous access was obtained using an 18-gauge cannula (Venflon 2, Ohmeda, Sweden), attached to a 6-inch I.V. posiflow connector (B·D PosiFlow, Becton Dickinson, USA). At each blood draw, the first 2 ml of blood was collected into a syringe and discarded. Then, for each draw, 13.5 ml of blood was collected into one tube (2 ml) containing potassium ethylenediaminetetracetic acid (EDTA K3E 15 %, 0.054 ml, Vacuette, Greiner Bio-one), two tubes (3 ml) containing sodium citrate (3.2% Buffered Sodium Citrate, Vacuette, Greiner Bio-one) and one tube (4.5 ml) containing citrate theophylline adenosine dipyridamole (CTAD, 3.2% Buffered Sodium Citrate, theophylline, adenosine, 0.3 ml dipyridamole, BD Vacutainer, Meylan Cedex). An additional clotted serum tube (Vacuette, Greiner Bio-one) was also taken during the initial draw on each participant's first visit. The cannula was maintained patent throughout the testing session by flushing with 2 ml of saline following each draw (0.9%, NaCl). All of the tubes were stored in melting ice until the end of the testing session. The clotted serum tube (5 ml) was sent to the biochemistry laboratory at City Hospital for liver and kidney function tests, blood glucose concentration, and a full lipid profile.

##### 2.2.2.6.2 Blood preparation and storage

Citrated blood was centrifuged at 1000 rpm for 10 minutes and then the supernatant, platelet-rich plasma (PRP), was aspirated and placed in a clear plastic centrifugation tube. A platelet count was performed using an automated haematology system (Advia 120, Bayer Diagnostics, USA) and the PRP was spun with the remaining citrate and

CTAD tubes at 3000 rpm for 20 minutes. The platelet-poor plasma (PPP) from the citrate, CTAD, and centrifugation tubes was aliquoted into individual vials, and stored at -70°C, for later analysis. The platelet pellet from the plastic centrifugation tube was re-suspended in sterile saline solution to give a platelet concentration 2 x $10^8$/ml.

The platelet adhesion assay [322] consisted of microtitre plates being coated with 100µl of fibrinogen and incubated overnight at 4°C. Any unbound fibrinogen was pipetted off and 100 µl of pooled platelet re-suspension solution was aliquoted into the microtitre wells and incubated for 60 minutes. The supernatant was aspirated and lysed using 100 µl of 5% phosphate-buffered saline (PBS) Tween and stored as supernatant platelet lysate (SPL). The wells were then carefully washed three times with saline, lysed with 5% PBS Tween, incubated for 30 minutes before the remaining solution was aspirated off and then stored as a bound plasma lysate (BPL). The remaining platelet re-suspension in the plastic centrifugation tube was lysed with 0.1% PBS Tween and aliquoted into individual vials to perform the platelet lysate assay.

#### 2.2.2.7 Blood analysis

##### 2.2.2.7.1 Full Blood Count (FBC)

Full blood count (FBC) was determined using an automated haematology system (Advia120, Bayer Diagnostics, USA), which provided measures of red blood cell (RBC) count (x $10^3$), white blood cell (WBC) count (x $10^3$), haemoglobin (Hb; g/dl), haematocrit (hct; %), total platelets (platelets; x $10^9$/l), mean platelet volume (MPV) (fl), mean platelet mass (MPM) (g/dl), lymphocytes (x $10^9$) neutrophils (x $10^9$/l), monocytes (x $10^9$/l).

2.2.2.7.2 von Willebrand Factor (vWF)

von Willebrand Factor (vWF) is a high-molecular weight procoagulant molecule (160kD) that has long been proposed as a marker of endothelium damage, and is of significant importance in haemostasis through its role in platelet-platelet and platelet-sub-endothelium adhesion. vWF was measured by commercially available ELISA (Dako, Glosrup, Denmark). Raised levels of vWF have been demonstrated in a variety of cardio- and cerebrovascular disorders such as stroke [323-324], heart failure [325-326], coronary artery disease [327], AF [328-329], and hypertension [330-331].

2.2.2.7.3 P-Selectin (CD62P)

P-selectin (CD62P, GMP-140, PADGEM) is a 140kD glycoprotein adhesion molecule which is a component of the cell-membrane within the alpha and dense granules [332], and Weibel-Palade bodies of the endothelial cells [333]. The membrane form of P-selectin has been shown to have a dual physiological role. Firstly, during inflammation, P-selectin is relocated onto the surface of activated endothelial cells where it mediates leukocyte rolling [334]. Secondly, in thrombosis, the expression of P-selectin in a thrombus supports the recruitment of leukocytes [332]. Soluble P-selectin (sP-sel) in plasma has been considered a marker of platelet activation [335] as P-selectin is proteolytically shed or actively cleaved from the cell surface (presumably by a non-specific enzyme or other mediator(s) that may arise from leukocytes, the endothelium, or else where) shortly after activation [335].

Soluble P-selectin levels in plasma, intra-platelet P-selectin levels from the SPL (stored from the lysate and un-bound step of the adhesion assay), and BPL (stored from bound step of the adhesion assay) were all measured by ELISA. Regents and

recombinant human P-selectin (as a standard) were obtained from R&D Systems (UK) Ltd (Abingdon, Oxon, UK). Levels of soluble P-selectin in plasma and the BPL were detected in a 1/5 dilution of phosphate-buffered saline, with the SPL being detected in a 1/10 dilution.

#### 2.2.2.7.4 E-Selectin (CD62E)

E-selectin (CD62E) is a cell-surface bound leukocyte adhesion molecule specific to endothelial cells. It mediates the interaction between leukocytes, platelets and the endothelium, and increased surface expression is thought to reflect endothelial activation [336]. The soluble form of E-selectin (sE-Sel) can be detected in healthy individuals, and although contradictory data exists, elevated levels have been found in patients with ischaemic heart disease [337], atherosclerosis [338], hypertension [339], and diabetes [340]. The only study to date to examining whether patients with AF had elevated levels of sE-selectin proved to be negative, demonstrating comparable levels compared to age- and sex-matched healthy controls in sinus rhythm [341].

Soluble E-selectin levels in plasma were measured by ELISA. Regents and recombinant human E-selectin (as a standard) were obtained from R&D Systems (UK) Ltd (Abingdon, Oxon, UK).

#### 2.2.2.7.5 Other markers

Total cholesterol (mmol/l) and triglycerides (mmol/l) were determined using a colometric system (Vitros 950, Johnson & Johnson, UK). High density lipoprotein (HDL) cholesterol was determined using the direct HDL method (Sigma E2 HDL Cholesterol, Sigma diagnostics, UK).

## 2.3 Data reduction and analysis

Data was analysed using SPSS for Windows (Version 12.0.1). All statistical tests were two tailed; p-values $\leq .05$ were considered statistically significant. All dichotomous variables were coded zero or one, were one signified a worse outcome. All categorical variables were compared using the chi-square statistic. The Yates continuity correction was used when there were expected frequencies of less than five in any cell.

### 2.3.1 Questionnaire study

Continuous variables were compared using independent t-tests; student's t-test for parametric analysis, and Mann Whitney-U test for non-parametric analysis. Quality-of-life data was analyzed using correlation and multiple linear regression. The demographic, clinical, and psychological variables that significantly correlated with quality of life at six-months were included in a multiple linear regression model. In such analyses, BDI and STAI were treated as both continuous and dichotomous variables. When both the continuous and dichotomous representation of a variable was significant, the continuous version was entered into the linear regression model.

### 2.3.2 Stress study

Continuous variables were compared using a one-way analysis of variance (ANOVA). The cardiovascular measurements (SBP, DBP, MAP, HR) obtained during baseline, task, 30- and 60-minute recovery period were averaged separately to yield mean values. A series of 4 time points (baseline, task, 30-minute recovery, 60-minute recovery) X 3 participant groups (AF patients, hypertensive patients, healthy controls) repeated-measures multivariate analyses of variance (MANOVAs) were

conducted for all cardiovascular, rheological, endothelial and platelet variables when participants attended in a euhydrated. For all MANOVAs measures of effect size ($\eta^2$) were reported. Main effects for time and time X participant group interactions were explored further using Bonferroni post-hoc comparisons. For the data presented in Tables and Figures 3.14 to 3.22, within-subject comparisons were undertaken using MANOVAs for parametric data and Friedman tests for non-parametric data, with between-subject comparison being undertaken using one-way ANOVAs and Kruskal-Wallis tests, respectively. Means (SD), standard error of the mean (SEM), and median (IQR) levels are reported where appropriate.

For each stress task, changes in plasma volume were calculated using the following formula: $\Delta$plasma volume = $100 \times (PVol_{Task} - PVol_{Baseline}) / PVol_{Baseline}$, where $PVol_{Baseline}$ is 100 minus baseline hematocrit [342]. The effect of postural-induced haemoconcentration on haemostatic markers was corrected for using the formula outlined below:

$$Cadjusted = Cunadjusted\ (1+(\triangle\ PVol/100)$$

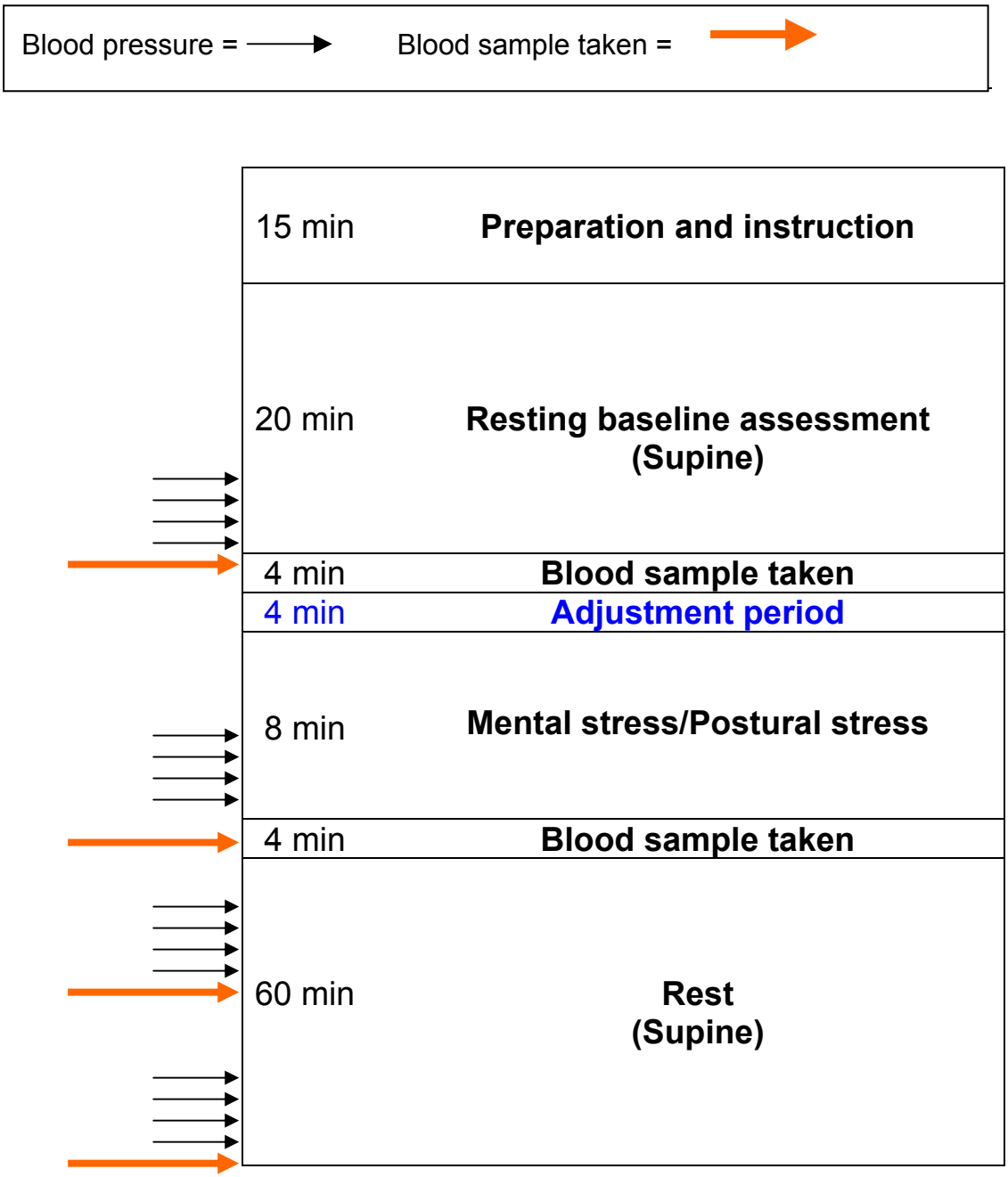
Cadjusted = concentration of marker when change in plasma volume have been accounted for

Cunadjusted = concentration of marker prior to correction for changes in plasma volume

To examine the effect of hydration status a series of 2 conditions (euhydrated, hyperhydrated) X 4 time points (baseline, task, 30-minute recovery, 60-minute recovery) MANOVAs were conducted on all cardiovascular, rheological, endothelial and platelet variables. Main effects for condition were explored further using paired

samples t-tests. When a significant effect of condition was observed a series of 2 condition (euhydrated, hyperhydrated) X 4 time points (baseline, task, 30-minute recovery, 60-minute recovery) X 3 participant groups (AF patients, hypertensive patients, healthy controls) MANOVAs were conducted.

Figure 2.1: Schematic representation of the procedure for the stress testing study



# CHAPTER 3

## Results

### 3.1 Questionnaire study

#### 3.1.1 Baseline characteristics of the eligible patients

##### 3.1.1.1 AF patients

The demographic and clinical characteristics for the 101 participating AF patients are summarised in Table 3.1. Also presented are the analogous data for the 93 patients who did not participate. With the exception of ethnicity, with Afro-Caribbean and South Asian patients more likely to refuse participation, no other significant differences in demographic and clinical characteristics between participants and non-participants were observed.

The mean (SD) age of the AF participants was 66.3 (11.0) years (range; 24-84 years). The majority of the participants were male (61.4%), Caucasian (89.7%), and not currently employed (70.1%). Further, most participants were likely to have either PAF (52.5%) or permanent AF (41.6%), with only a small percentage having persistent AF (5.9%). The median (IQR) duration of AF was 21 months (range; 8-49 months). Hypertension was the most common coexisting cardiovascular co-morbidity (88.1%), followed by diabetes (10.9%). With regards to medication, the majority of patients were receiving some form of anti-coagulant (warfarin 72.3%) or anti-platelet therapy (22.8%) (see Table 3.1).

Table 3.1: Demographic and clinical characteristics of the 194 eligible AF patients

| | **Participants** (n = 101) | **Non-participants** (n = 93) | ***Z*** | ***t*** | $x^2$ | ***p*** |
|---|---|---|---|---|---|---|
| *Demographic characteristics, n (%)* | | | | | | |
| **Mean (SD) age,** Years | 66.3 (11.0) | 68.7 (10.6) | | -1.52 | | .13 |
| **Males** | 62 (61.4) | 54 (55.7) | | | .10 | .75 |
| **Ethnicity** | | | | | | |
| Caucasian | 96 (95.1) | 77 (82.8) | | | | |
| Afro-Caribbean | 3 (3.0) | 7 (7.5) | | | 7.83 | **.02** |
| South-Asian | 2 (2.0) | 9 (9.7) | | | | |
| **Occupational Status** Employed | 38 (37.6) | 23 (24.7) | | | 3.20 | .08 |
| **Mean (SD) deprivation score** | 4.37 (3.80) | 4.78 (4.07) | | .88 | | .38 |
| *Clinical characteristics, n (%)* | | | | | | |
| **Type of AF** | | | | | | |
| Paroxysmal | 53 (52.5) | 38 (40.9) | | | | |
| Persistent | 6 (5.9) | 9 (9.7) | | | | |
| Permanent | 42 (41.6) | 46 (49.5) | | | 2.93 | .23 |
| **Median (IQR) Duration of AF,** Months | 21 (8 – 49) | 18 (8 – 54) | .64 | | | .52 |
| **Hypertension** | 89 (88.1) | 79 (84.9) | | | .19 | .66 |
| **Diabetes** | 11 (10.9) | 16 (17.2) | | | 1.58 | .21 |
| **Myocardial Infarction** | 6 (5.9) | 5 (5.4) | | | .00 | .87 |
| **Heart Failure** | 3 (3.0) | 6 (6.4) | | | .66 | .42 |
| **Stroke** | 6 (5.9) | 4 (4.3) | | | .04 | .85 |
| **Transient Ischemic Attack** | 6 (5.9) | 7 (7.5) | | | .02 | .88 |
| *Current medication, n (%)* | | | | | | |
| **Warfarin** | 75 (74.3) | 63 (67.7) | | | .71 | .40 |
| **Antiplatelet** | 22 (22.8) | 31 (33.3) | | | 2.7 | .10 |
| **Digoxin** | 26 (25.7) | 30 (32.2) | | | .71 | .40 |
| **Calcium Channel Blockers** | 49 (48.5) | 37 (39.8) | | | 1.2 | .28 |
| **Beta-Blocker** | 56 (55.4) | 50 (53.8) | | | .00 | .93 |
| **Angiotensin-converting-enzyme (ACE) inhibitor** | 32 (31.7) | 36 (38.7) | | | .76 | .38 |
| **Statin** | 30 (29.7) | 24 (25.8) | | | .20 | .66 |

#### 3.1.1.2 Hypertensive patients

The demographic and clinical characteristics for the 97 participating hypertensive patients are summarised in Table 3.2. Also presented are the analogous data for the 63 hypertensive patients who were unwilling to participate. Once again, Afro-Caribbean and South Asian patients were more likely to refuse participation. No other significant differences in demographic and clinical characteristics were observed.

The mean (SD) age of the hypertensive participants was 68.0 (7.2) years (range; 50-84 years). The majority of the participants were male (61.4%), Caucasian (89.7%), and not currently employed (70.1%). Diabetes was the most common coexisting cardiovascular co-morbidity (49.5%), followed by a history of MI (10.3%). With regards to medication, less than half of the patients were receiving anti-platelet therapy (43.3%), in combination with a variety of other pharmacological agents

Table 3.2: Demographic and clinical characteristics of the 160 eligible hypertensive patients

| | **Participant** (n = 97) | **Non-participants** (n = 63) | ***t*** | ***$x^2$*** | ***p*** |
|---|---|---|---|---|---|
| *Demographic characteristics, n (%)* | | | | | |
| **Mean (SD) age,** Years | 68.0 (7.2) | 68.9 (7.5) | .80 | | .43 |
| **Males** | 64 (66.0) | 42 (66.7) | | .00 | 1.00 |
| **Ethnicity** | | | | | |
| Caucasian | 87 (89.7) | 48 (76.2) | | | |
| Afro-Caribbean | 9 (9.3) | 7 (11.1) | | 10.20 | **<.01** |
| South-Asian | 1 (1.0) | 8 (12.7) | | | |
| **Occupational Status** Employed | 29 (29.9) | 16 (25.4) | | .19 | .66 |
| **Mean (SD) deprivation score** | 4.74 (3.6) | 4.80 (3.9) | .10 | | .92 |
| *Clinical characteristics, n (%)* | | | | | |
| **Diabetes** | 48 (49.5) | 35 (55.6) | | .35 | .56 |
| **Myocardial Infarction** | 10 (10.3) | 6 (9.5) | | .00 | 1.00 |
| **Heart Failure** | 2 (2.1) | 0 (0.0) | | .18 | .68 |
| **Stroke** | 5 (5.2) | 2 (3.2) | | .04 | .84 |
| **Transient Ischemic Attack** | 6 (6.2) | 1 (1.6) | | 1.00 | .32 |
| *Current medication, n (%)* | | | | | |
| **Warfarin** | 2 (2.1) | (3.2) | | .00 | 1.00 |
| **Antiplatelet** | 42 (43.3) | 19 (30.2) | | 2.30 | .13 |
| **Diuretic** | 51 (52.6) | 29 (43.0) | | .42 | .52 |
| **Calcium channel blocker** | 39 (40.2) | 30 (47.6) | | .58 | .45 |
| **Beta–blocker** | 49 (50.5) | 32 (50.8) | | .00 | 1.00 |
| **Alpha-blocker** | 53 (54.6) | 35 (52.2) | | .00 | 1.00 |
| **Angiotensin converting enzyme (ACE) inhibitor** | 42 (43.3) | 25 (37.3) | | .08 | .77 |
| **Angiotensin II receptor blocker** | 13 (13.4) | 8 (11.9) | | .00 | 1.00 |
| **Statin** | 57 (58.8) | 28 (41.2) | | 2.60 | .11 |

### 3.1.2 Demographic, clinical, and psychological characteristics of AF and hypertensive participants

The demographic, clinical, and psychological characteristics of the 101 AF patients and 97 hypertensive patients are summarised in Table 3.3. No significant differences were observed in age, sex, ethnicity, occupational status, and deprivation score between the AF and hypertensive patients. Although the hypertensive patients were more likely to have diabetes, the number of other cardiovascular co-morbidities was not significantly different between the two patient groups. Both patient groups displayed similar levels of depression, state anxiety (mean score and percentage of scores $\geq$ 10 on BDI and $\geq$ 40 on STAI), and QoL. However, higher levels of trait anxiety (mean score and percentage of scores $\geq$ 40 on STAI) were observed in the AF patients. No significant differences in any of the psychological parameters were observed between PAF and permanent AF patients (data not shown).

### 3.1.3 Baseline characteristics of the depressed (BDI score $\geq$10) and non-depressed (BDI score <10) AF participants

The demographic and clinical characteristics of the 38 (37.6%) depressed and 63 (62.4%) non-depressed AF patients are summarised in Table 3.4. No significant differences in age, sex, ethnicity, occupational status, and deprivation score were observed between the depressed and non-depressed AF patients. Depressed patients displayed higher levels of state and trait anxiety (mean score and percentage of scores $\geq$ 40 on STAI) and reported lower QoL.

Table 3.3: Demographic, clinical, and psychological characteristics of the AF and hypertensive patients

| | **AF patients** (n= 101) | **Hypertensive patients** (n=97) | ***Z*** | ***t*** | $X^2$ | ***p*** |
|---|---|---|---|---|---|---|
| *Demographic characteristics, n (%)* | | | | | | |
| **Mean (SD) age,** Years | 66.3 (11.0) | 68.0 (7.2) | | 1.2 | | .23 |
| **Males** | 62 (61.4) | 64 (66.0) | | | .46 | .50 |
| **Ethnicity** | | | | | | |
| White | 96 (95.0) | 87 (89.7) | | | | |
| Afro-Caribbean | 3 (3.0) | 9 (9.3) | | | 2.87 | .24 |
| South-Asian | 2 (2.0) | 1 (1.0) | | | | |
| **Occupational Status** | 38 (37.6) | 29.9 (29.9) | | | .71 | .40 |
| **Mean (SD) deprivation score** | 4.37 (3.8) | 4.74 (3.6) | | .56 | | .58 |
| *Clinical characteristics, n (%)* | | | | | | |
| **Significant co-morbidity** | | | | | | |
| One | 57 (56.4) | 50 (51.5) | | | | |
| Two or more | 39 (38.6) | 20 (20.6) | | | 2.07 | .15 |
| **Hypertension,** | 89 (88.1) | 97 (100) | | | 10.27 | **<.01** |
| **Diabetes** | 11 (10.9) | 47 (48.5) | | | 31.92 | **<.01** |
| **Myocardial Infarction,** | 6 (5.9) | 11 (11.3) | | | 1.21 | .27 |
| **Stroke** | 6 (5.9) | 5 (5.2) | | | .00 | 1.00 |
| **Transient Ischemic Attack** | 6 (5.9) | 6 (6.2) | | | .00 | 1.00 |
| *Psychological characteristics, n (%)* | | | | | | |
| **Median (IQR) BDI score** | 7.0 (3 – 13) | 6.0 (2 – 10) | -1.83 | | | .07 |
| **BDI score ≥10** | 38 (37.6) | 29 (30.0) | | | 1.00 | .32 |
| **Mean (SD) State Anxiety score** | 35.2 (12.3) | 32.0 (12.0) | | 1.85 | | .06 |
| **State Anxiety score ≥40,** | 28 (27.7) | 22 (22.7) | | | .23 | .63 |
| **Mean (SD) Trait Anxiety score** | 37.4 (12.6) | 33.3 (11.4) | | 2.36 | | **.02** |
| **Trait Anxiety score ≥40,** | 38 (37.6) | 21 (21.6) | | .45 | | **.03** |
| **Mean (SD) QoL score** | 20.4 (5.7) | 19.9 (5.3) | | .58 | | .57 |

Table 3.4: Demographic, clinical, and psychological characteristics of the depressed and non-depressed AF patients

| | **Depressed** (n=38) | **Non-depressed** (n=63) | $x^2$ | ***T*** | ***P*** |
|---|---|---|---|---|---|
| *Demographic characteristics, n (%)* | | | | | |
| **Mean (SD) age,** Years | 65.8 (10.1) | 66.6 (11.5) | | .34 | .73 |
| **Males** | 23 (60.5) | 39 (61.9) | .00 | | 1.00 |
| **Ethnicity** | | | | | |
| Caucasian | 38 (100.0) | 58 (92.1) | | | |
| Afro-Caribbean | 0 (0.0) | 3 (5.0) | | | |
| South-Asian | 0 (0.0) | 2 (3.2) | 3.17 | | .21 |
| **Occupational Status** | | | | | |
| Employed | 14 (36.9) | 24 (38.1) | .00 | | 1.00 |
| **Mean (SD) deprivation score** | 4.0 (4.1) | 4.5 (3.6) | | .72 | .48 |
| *Clinical characteristic, n (%)* | | | | | |
| **Type of AF** | | | | | |
| PAF | 21 (55.3) | 33 (48.5) | | | |
| Persistent | 1 (2.6) | 5 (7.9) | 1.41 | | .49 |
| Permanent | 17 (44.7) | 25 (36.8) | | | |
| **Significant co-morbidity** | | | | | |
| One | 16 (42.1) | 41 (65.1) | | | |
| Two or more | 19 (50.0) | 20 (31.7) | 3.42 | | .65 |
| *Psychological characteristics* | | | | | |
| **Mean (SD) state anxiety score** | 43.3 (13.5) | 30.4 (8.5) | | 5.91 | **<.01** |
| **State Anxiety score ≥40** | 20 (52.6) | 8 (12.7) | 16.90 | | **<.01** |
| **Mean (SD) Trait Anxiety Score** | 47.3 (12.3) | 31.4 (8.4) | | 7.71 | **<.01** |
| **State Anxiety score ≥40** | 27 (71.1) | 11 (17.5) | 26.77 | | **<.01** |
| **Mean (SD) QoL score** | 23.4 (5.3) | 18.5 (5.1) | | 4.55 | **<.01** |

### 3.1.4 Baseline characteristics of the anxious and non-anxious AF participants

#### 3.1.4.1 State anxiety

The demographic and clinical characteristics of the 28 (27.7%) anxious and 68 (72.3%) non-anxious AF patients are summarised in Table 3.5. No significant group differences were observed between the anxious and non-anxious patients. Anxious patients reported higher levels of depression (mean and number of scores ≥ 10 on BDI), trait anxiety (mean level and number of scores ≥ 40 on STAI), and had a lower QoL.

Table 3.5: Demographic, clinical, and psychological characteristics of the anxious and non-anxious (state) AF patients

| | **Anxious** (n=28) | **Non-Anxious** (n=73) | ***Z*** | ***t*** | $x^2$ | ***P*** |
|---|---|---|---|---|---|---|
| *Demographic characteristics, n (%)* | | | | | | |
| **Mean (SD) age,** Years | 63.5 (12.8) | 67.4 (10.1) | | 1.60 | | .11 |
| **Males** | 16 (57.1) | 46 (63.0) | | | .10 | .75 |
| **Ethnicity** | | | | | | |
| Caucasian | 28 (100.0) | 68 (93.2) | | | | |
| Afro-Caribbean | 0 (0.0) | 3 (4.1) | | | | |
| South-Asian | 0 (0.0) | 2 (2.7) | | | 2.02 | .37 |
| **Occupational Status** Employed | 12 (42.9) | 26 (35.6) | | | .20 | .66 |
| **Mean (SD) deprivation score** | 3.9 (4.4) | 4.6 (3.5) | | .79 | | .43 |
| *Clinical characteristics, n (%)* | | | | | | |
| **Type of AF** | | | | | | |
| PAF | 13 (46.4) | 40 (54.8) | | | | |
| Persistent | 1 (3.6) | 5 (6.8) | | | | |
| Permanent | 14 (50.0) | 28 (38.4) | | | 1.30 | .52 |
| **Significant co-morbidity** | | | | | | |
| One | 13 (52.0) | 44 (62.0) | | | | |
| Two or more | 12 (48.0) | 27 (38.0) | | | .41 | .53 |
| *Psychological characteristics, n (%)* | | | | | | |
| **Median (IQR) BDI score** | 15.5 (8 – 22) | 6.0 (3 – 10) | -5.15 | | | **<.01** |
| **BDI score ≥10** | 20 (71.4) | 18 (24.7) | | | 16.92 | **<.01** |
| **Mean (SD) trait anxiety score** | 51.9 (8.4) | 31.8 (9.0) | | -10.20 | | **<.01** |
| **Trait Anxiety score ≥40** | 27 (96.4) | 11 (15.1) | | | 53.70 | **<.01** |
| **Mean (SD) QoL score** | 23.7 (5.5) | 19.1 (5.2) | | -3.91 | | **<.01** |

#### 3.1.4.2 Trait anxiety

The demographic and clinical characteristics of the 29 (28.7%) anxious and 68 (67.3%) non-anxious AF patients are summarised in Table 3.6. With the exception of age, with younger AF patients displaying greater levels of anxiety, no other significant group differences were observed for sex, ethnicity, occupational status, and deprivation score. Anxious patients reported higher levels of depression (mean and number of scores $\geq$ 10 on BDI), state anxiety (mean level and number of scores $\geq$ 40 on STAI), and had a lower QoL.

### 3.1.5 Baseline characteristics of the depressed (BDI score $\geq$ 10) and non-depressed (BDI score < 10) hypertensive participants

The demographic and clinical characteristics of the 29 (30.0%) depressed and the 68 (70.0%) non-depressed hypertensive patients are summarised in Table 3.7. No significant group differences were observed for age, sex, ethnicity, occupational status, and deprivation score between the depressed and non-depressed hypertensive patients. As with the AF patients, depressed hypertensive patients displayed higher levels of state and trait anxiety (mean score and number of scores $\geq$ 40 on STAI), and reported a lower QoL.

Table 3.6: Demographic, clinical, and psychological characteristics of the anxious and non-anxious (trait) AF patients

| | **Anxious** (n=38) | **Non-Anxious** (n=63) | ***Z*** | ***t*** | $x^2$ | ***P*** |
|---|---|---|---|---|---|---|
| *Demographic characteristics, n (%)* | | | | | | |
| **Mean (SD) age,** Years | 63.0 (13.7) | 68.3 (8.5) | | 2.42 | | **.02** |
| **Males** | 22 (58.0) | 40 (63.5) | | | .12 | .73 |
| **Ethnicity** | | | | | | |
| Caucasian | 37 (97.4) | 59 (93.7) | | | | |
| Afro-Caribbean | 0 (0.)) | 3 (4.8) | | | | |
| South-Asian | 1 (2.6) | 1 (1.5) | | | 1.98 | .37 |
| **Occupational Status** Employed | 14 (36.9) | 24 (38.1) | | | .00 | 1.00 |
| **Mean (SD) deprivation score** | 3.9 (4.0) | 4.7 (3.7) | | .99 | | .32 |
| *Clinical characteristics, n (%)* | | | | | | |
| **Type of AF** | | | | | | |
| PAF | 19 (50.0) | 34 (54.0) | | | | |
| Persistent | 1 (2.6) | 4 (7.9) | | | | |
| Permanent | 18 (47.4) | 24 (38.1) | | | 1.68 | .43 |
| **Significant co-morbidity** | | | | | | |
| One | 18 (47.4) | 39 (61.9) | | | | |
| Two or more | 17 (44.7) | 22 (34.9) | | | .97 | .33 |
| *Psychological characteristics, n (%)* | | | | | | |
| **Median (IQR) BDI score** | 14.5 (8 – 21) | 5.0 (2 – 8) | -6.12 | | | **<.01** |
| **BDI score ≥10** | 27 (71.1) | 11 (17.5) | | | 27.77 | **<.01** |
| **Mean (SD) state anxiety score** | 46.7 (11.2) | 28.3 (6.2) | | 10.70 | | **<.01** |
| **State Anxiety score ≥40** | 27 (71.1) | 1 (1.6) | | | 53.70 | **<.01** |
| **Mean (SD) QoL score** | 23.5 (5.6) | 18.5 (4.8) | | 4.55 | | **<.01** |

Table 3.7: Demographic, clinical, and psychological characteristics of the depressed and non-depressed hypertensive patients

| | **Depressed** (n=29) | **Non-depressed** (n=68) | $X^2$ | *t* | *P* |
|---|---|---|---|---|---|
| *Demographic characteristics, n (%)* | | | | | |
| **Mean (SD) age,** Years | 66.2 (7.6) | 68.6 (6.9) | | 1.48 | .14 |
| **Males** | 15 (51.7) | 50 (73.5) | 3.44 | | .06 |
| **Ethnicity** | | | | | |
| Caucasian | 25 (86.2) | 65 (95.6) | | | |
| Afro-Caribbean | 3 (10.3) | 3 (4.4) | | | |
| South-Asian | 1 (3.4) | 0 (0.0) | 2.66 | | .27 |
| **Occupational Status** | | | | | |
| Employed | 9 (31.0) | 21 (30.9) | .00 | | 1.00 |
| **Mean (SD) deprivation score** | 4.4 (3.6) | 4.8 (3.5) | | .56 | .58 |
| *Clinical characteristics, n (%)* | | | | | |
| **Significant co-morbidity** | | | | | |
| One | 16 (55.2) | 34 (50.0) | | | |
| Two or more | 8 (27.6) | 12 (17.6) | .13 | | .72 |
| **Diabetes** | 15 (51.7) | 32 (47.1) | .04 | | .84 |
| *Psychological characteristics* | | | | | |
| **Mean (SD) state anxiety score** | 43.5 (12.3) | 27.1 (7.8) | | 7.80 | **<.01** |
| **State Anxiety score ≥40** | 16 (55.2) | 6 (8.8) | 22.30 | | **<.01** |
| **Mean (SD) Trait Anxiety score** | 44.4 (11.3) | 28.5 (7.4) | | 8.07 | **<.01** |
| **Trait Anxiety score ≥40** | 17 (58.6) | 4 (5.9) | 30.30 | | **<.01** |
| **Mean (SD) QoL score** | 23.1 (5.4) | 18.4 (4.6) | | 4.33 | **<.01** |

### 3.1.6 Baseline characteristics of the anxious and non-anxious hypertensive participants

#### 3.1.6.1 State anxiety

The demographic and clinical characteristics of the 22 (22.7%) anxious and 68 (73.3%) non-anxious hypertensive patients are summarised in Table 3.8. With the exception of age, with younger hypertensive patients displaying greater levels of anxiety, no other significant differences were observed in, sex, ethnicity, occupational status, and deprivation score between the anxious and non-anxious patients. Anxious patients

reported higher levels of depression (mean and number of scores ≥ 10 on BDI), trait anxiety (mean level and number of scores ≥ 40 on STAI), and had a lower QoL.

Table 3.8: Demographic, clinical, and psychological characteristics of the anxious and non-anxious (state) hypertensive patients

| | **Anxious** (n=22) | **Non-Anxious** (n=71) | ***Z*** | ***t*** | $x^2$ | ***p*** |
|---|---|---|---|---|---|---|
| *Demographic characteristics, n (%)* | | | | | | |
| **Mean (SD) age,** Years | 64.3 (8.5) | 68.6 (6.2) | | 2.58 | | **<.01** |
| **Males** | 11 (50.0) | 53 (74.6) | | | 3.67 | .06 |
| **Ethnicity** | | | | | | |
| Caucasian | 20 (90.9) | 64 (90.1) | | | | |
| Afro-Caribbean | 1 (4.5) | 7 (9.9) | | | | |
| South-Asian | 1 (4.5) | 0 (0.0) | | | 3.51 | .15 |
| **Occupational Status** | | | | | | |
| Employed | 10 (45.4) | 20 (28.2) | | | 2.10 | .21 |
| **Mean (SD) deprivation score** | 4.1 (3.8) | 4.8 (3.4) | | .83 | | .41 |
| *Clinical characteristics, n (%)* | | | | | | |
| **Significant co-morbidity** | | | | | | |
| One | 12 (63.2) | 36 (75.0) | | | | |
| Two or more | 7 (36.8) | 12 (25.0) | | | .45 | .50 |
| *Psychological characteristics, n (%)* | | | | | | |
| **Median (IQR) BDI score** | 13.0 (9 – 17) | 5.0 (2 – 8) | -5.05 | | | **<.01** |
| **BDI score ≥10** | 16 (72.7) | 12 (16.9) | | | 22.29 | **<.01** |
| **Mean (SD) trait anxiety score** | 48.0 (10.1) | 28.8 (7.1) | | -9.94 | | **<.01** |
| **Trait Anxiety score ≥40** | 16 (72.7) | 5 (7.0) | | | 37.78 | **<.01** |
| **Mean (SD) QoL score** | 24.6 (5.2) | 18.2 (4.3) | | -5.78 | | **<.01** |

### 3.1.6.2 Trait anxiety

The demographic and clinical characteristics of the 21 (21.6%) anxious and 72 (74.2%) non-anxious hypertensive patients are summarised in Table 3.9. No significant group differences were observed for ethnicity, occupational status, and deprivation score.

However, the anxious patients were more likely to be younger and female. Anxious patients also displayed higher levels of depression (mean and number of scores ≥ 10 on BDI), state anxiety (mean level and number of scores ≥ 40 on STAI), and reported a lower QoL.

Table 3.9: Demographic, clinical, and psychological characteristics of the anxious and non-anxious (trait) hypertensive patients

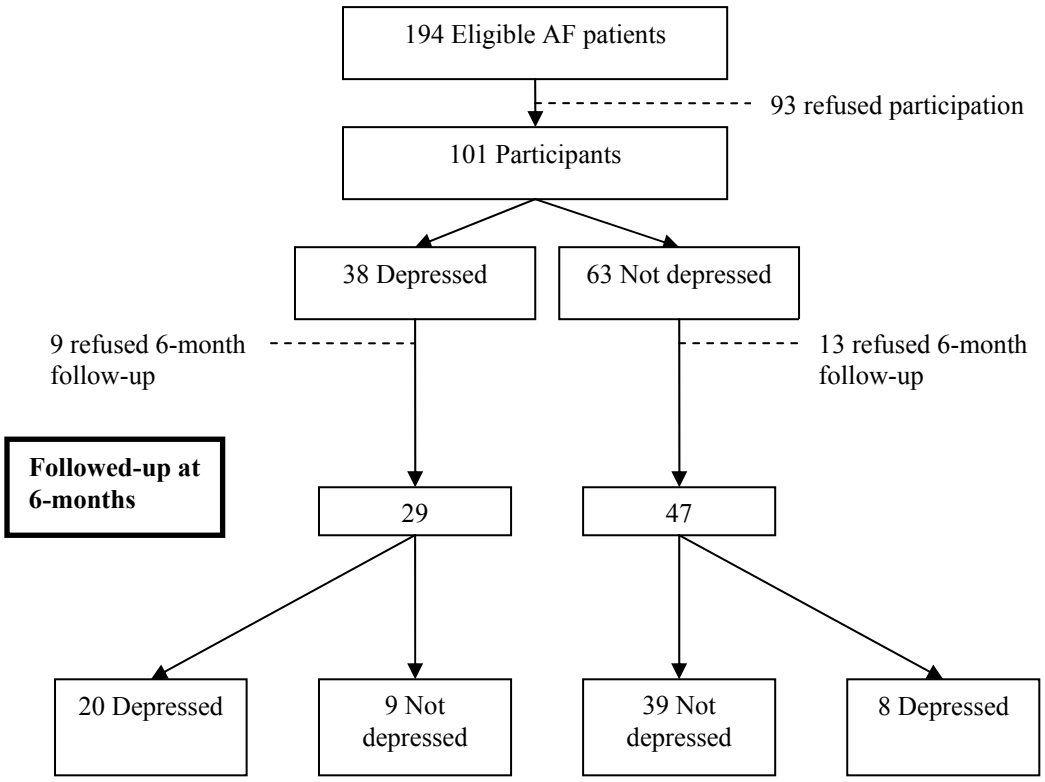
| | **Anxious** (n=21) | **Non-Anxious** (n=72) | ***Z*** | ***T*** | $X^2$ | ***P*** |
|---|---|---|---|---|---|---|
| *Demographic characteristics* | | | | | | |
| **Mean (SD) age,** Years | 63.4 (7.9) | 68.8 (6.3) | | 3.25 | | **<.01** |
| **Males** | 7 (33.3) | 57 (79.2) | | | 13.90 | **<.01** |
| **Ethnicity** | | | | | | |
| Caucasian | 18 (85.7) | 66 (91.7) | | | | |
| Afro-Caribbean | 2 (9.5) | 6 (8.3) | | | | |
| South-Asian | 1 (4.8) | 0 (0.0) | | | 3.52 | .17 |
| **Occupational Status** Employed; N, (%) | 10 (47.6) | 20 (27.8) | | | 2.10 | .15 |
| **Mean (SD) deprivation score** | 4.9 (4.0) | 4.6 (3.4) | | .29 | | .77 |
| *Clinical characteristics* | | | | | | |
| **Significant co-morbidity** | | | | | | |
| One | 11 (52.4) | 37 (51.4) | | | | |
| Two or more | 5 (23.8) | 14 (19.4) | | | .00 | 1.00 |
| *Psychological characteristics* | | | | | | |
| **Median (IQR) BDI score** | 13.0 (11 – 18) | 5.0 (2 – 8) | -6.00 | | | **<.01** |
| **BDI score ≥10** | 17 (81.0) | 11 (15.3) | | | 30.30 | **<.01** |
| **Mean (SD) state anxiety score** | 48.1 (11.3) | 27.3 (7.2) | | 10.13 | | **<.01** |
| **State Anxiety score ≥40,** N, | 16 (76.2) | 6 (7.2) | | | 37.80 | **<.01** |
| **Mean (SD) QoL score** | 25.1 (5.1) | 18.2 (4.2) | | 6.21 | | **<.01** |

### 3.1.7 Persistence of depression over the six-month follow-up period

#### 3.1.7.1 AF patients

The persistence of depression in AF patients over the initial six-month follow-up is depicted in Figure 3.1. The median (IQR) BDI score at baseline was 7.0 (3.0 – 13.0), with 38 (37.6%) patients reporting significant levels of depressive symptoms (BDI score $\geq$ 10). The BDI was returned and completed at six-months by 76 (75.2%) AF patients; the median (IQR) BDI score was 7.0 (3.0 – 12.8). Of these patients, depression was present at follow-up in 28 (36.8%) individuals. Of the AF patients depressed at baseline, 52.6% continued to report significant depressive symptoms at six-months.

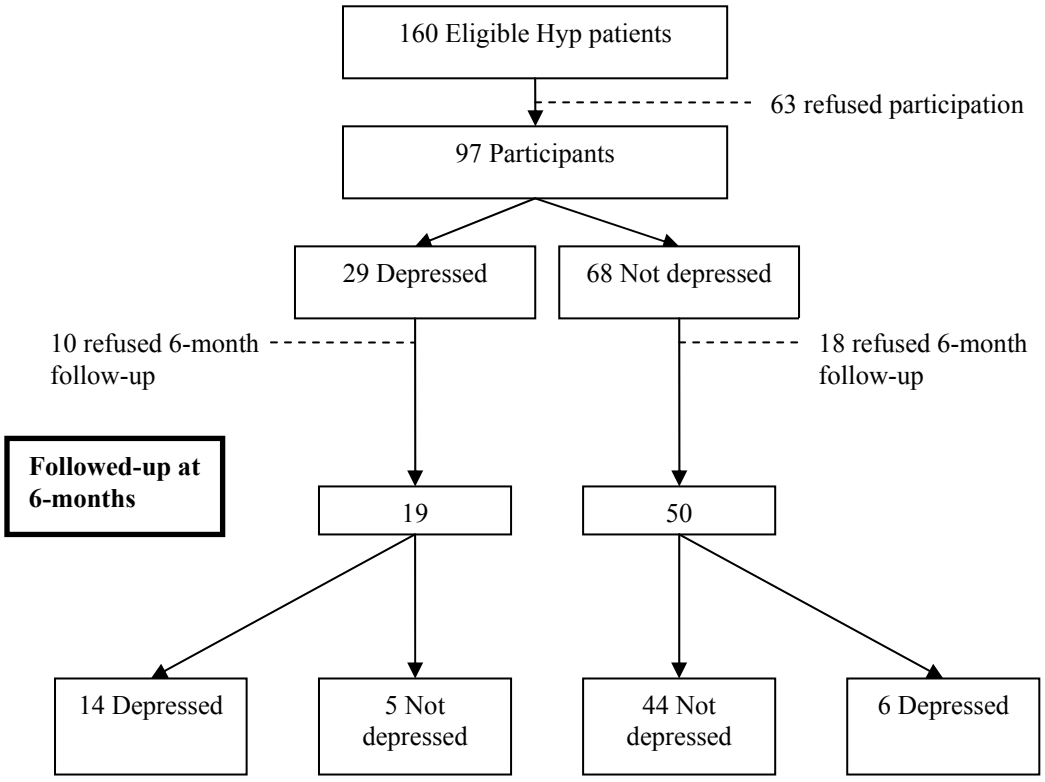
Figure 3.1: Persistence of depression over the six-month follow-up period in patients with AF



3.1.7.2 Hypertensive patients

The persistence of depression in hypertensive patients over the initial six-month follow-up is depicted in Figure 3.2. The median (IQR) BDI score at baseline was 6.0 (2 – 10), with 29 (30.0%) patients reporting significant depressive symptoms (BDI score $\geq$ 10). The BDI was returned and completed at six-months by 68 (70.1%) patients with hypertension; the median (IQR) BDI score was 6.0 (2.25 – 10.75). Of these patients, depression was apparent at follow-up in 20 individuals (29.4%). Of the hypertensive patients depressed at baseline, 48.3% continued to report significant depressive symptoms at six-months.

Figure 3.2: Persistence of depression over the six-month follow-up period in patients with hypertension

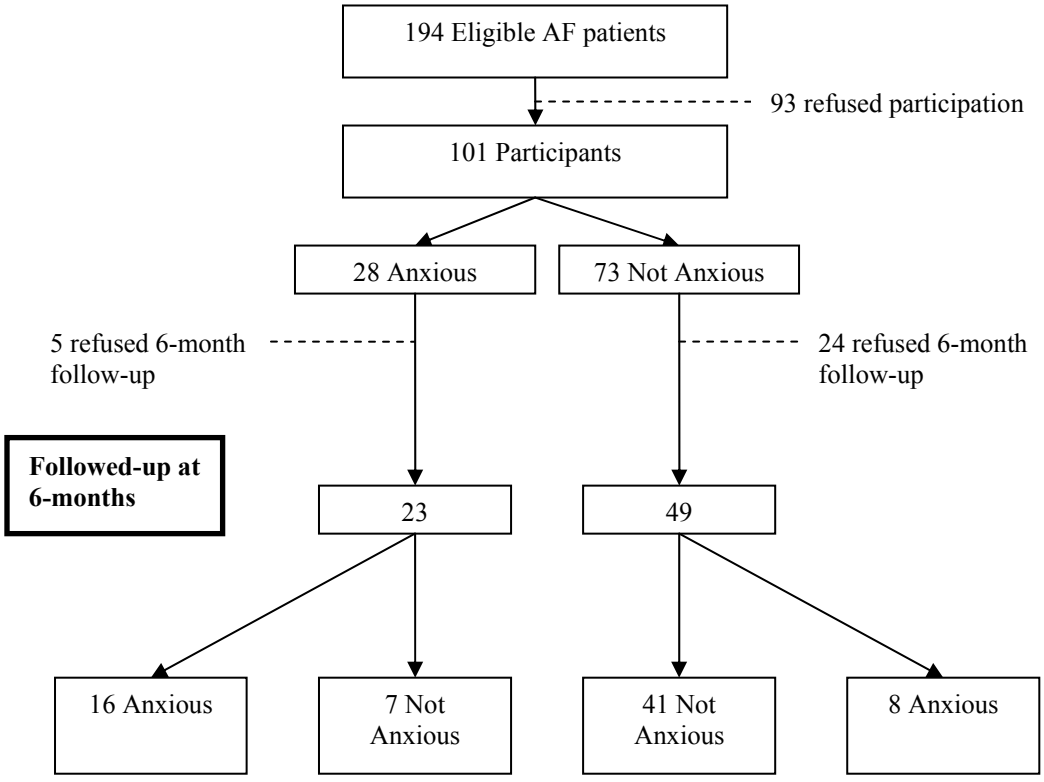


### 3.1.8 Persistence of anxiety over the six-month follow-up period

#### 3.1.8.1 State anxiety in AF patients

The persistence of state anxiety in AF patients over the initial six-month follow-up is depicted in Figure 3.3. The mean (SD) state anxiety score at baseline was 35.2 (12.3), with 28 (27.7%) patients reporting high levels of state anxiety (STAI-S scores $\geq$ 40). The STAI-S was returned and completed at six-months by 72 (71.3%) patients; the mean (SD) score was 35.6 (12.3). Of these patients, high levels of state anxiety were present at follow-up in 24 individuals (33.3%). Of the AF patients reporting high levels of state anxiety at baseline, 57.1% continued to report elevated scores at six-months.

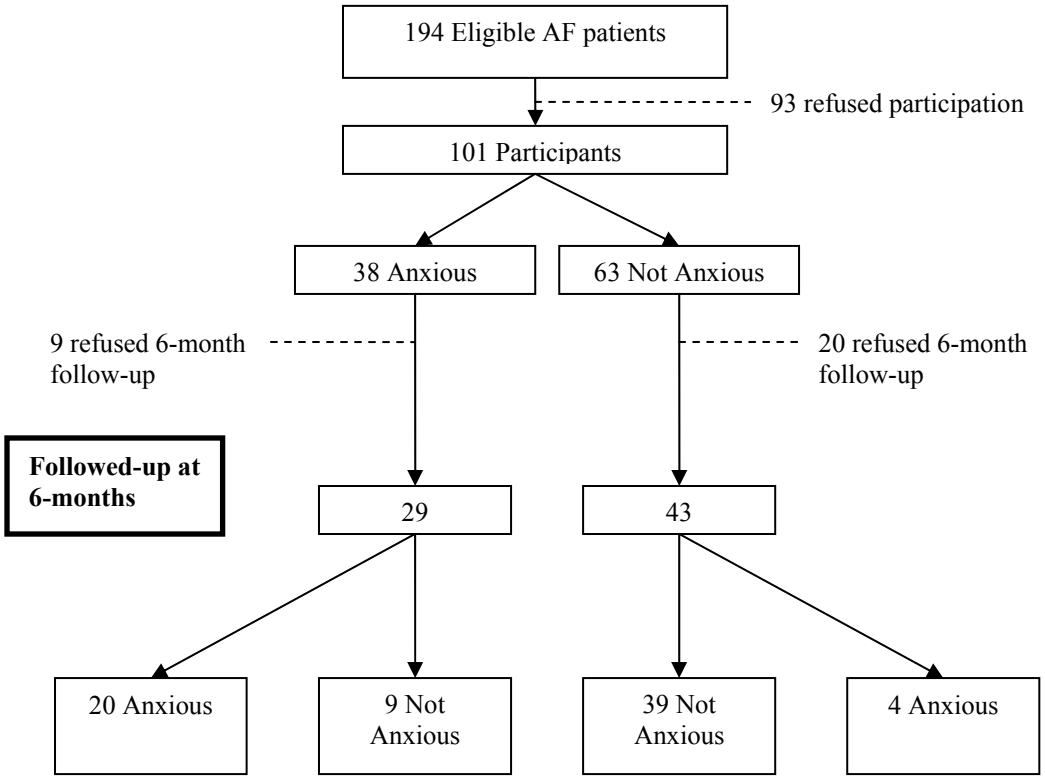
Figure 3.3: Persistence of state anxiety over the six-month follow-up period in patients with AF



3.1.8.2 Trait anxiety in AF patients

The persistence of trait anxiety in AF patients over the initial six-month follow-up is depicted in Figure 3.4. The mean (SD) trait anxiety score at baseline was 37.4 (12.6), with 38 (37.6%) patients reporting high levels of trait anxiety (STAI-T scores $\geq$ 40). The STAI-T was returned and completed at six-months by 72 (71.3%) patients; the mean (SD) score was 36.9 (12.5). Of these patients, high levels of trait anxiety were apparent at follow-up in 24 individuals (33.3%). Of the AF patients reporting high levels of trait anxiety at baseline, 52.6% continued to report high levels at six-months.

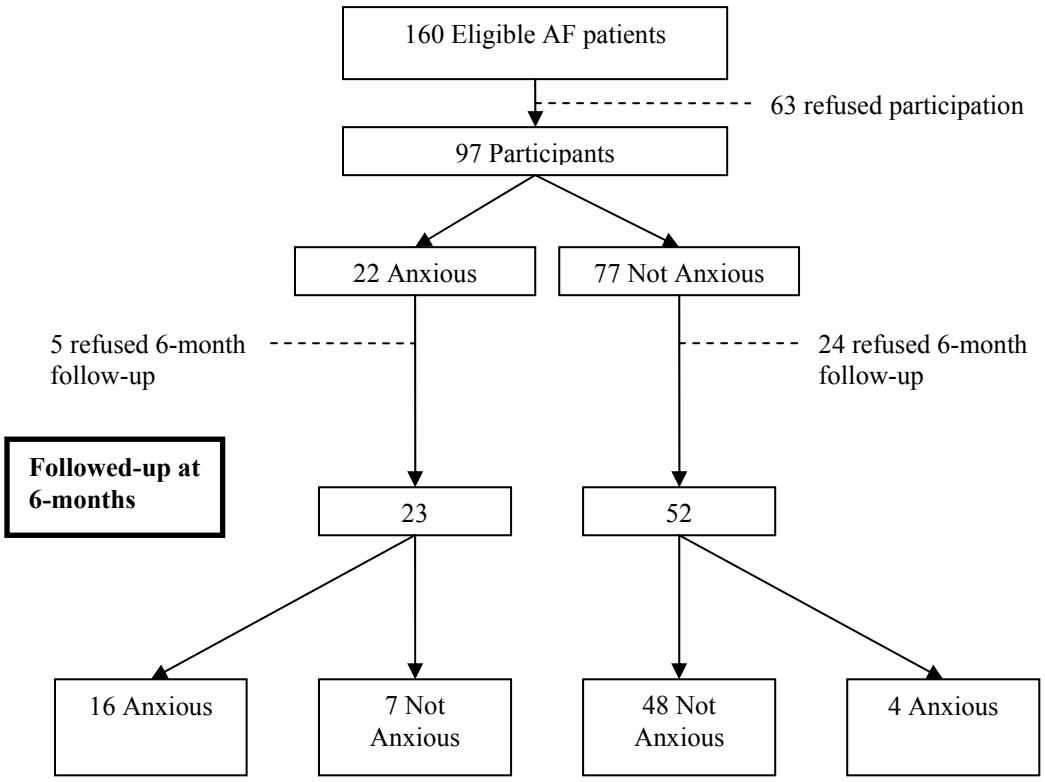
Figure 3.4: Persistence of trait anxiety over the six-month follow-up in patients with AF



3.1.8.3 State anxiety in hypertensive patients

The persistence of state anxiety in hypertensive patients over the initial six-month follow-up is depicted in Figure 3.5. The mean (SD) state anxiety score at baseline was 32.0 (12.0), with 22 (22.7%) patients reporting high levels of state anxiety (STAI-S scores $\geq$ 40). The STAI-S was returned and completed at six-months by 67 (69.2%) patients; the mean (SD) score was 31.61 (11.9). Of these patients, high levels of state anxiety were present at follow-up in 24 (33.3%) individuals. Of the hypertensive patients reporting high levels of state anxiety at baseline, 57.1% continued to report high levels at six-months.

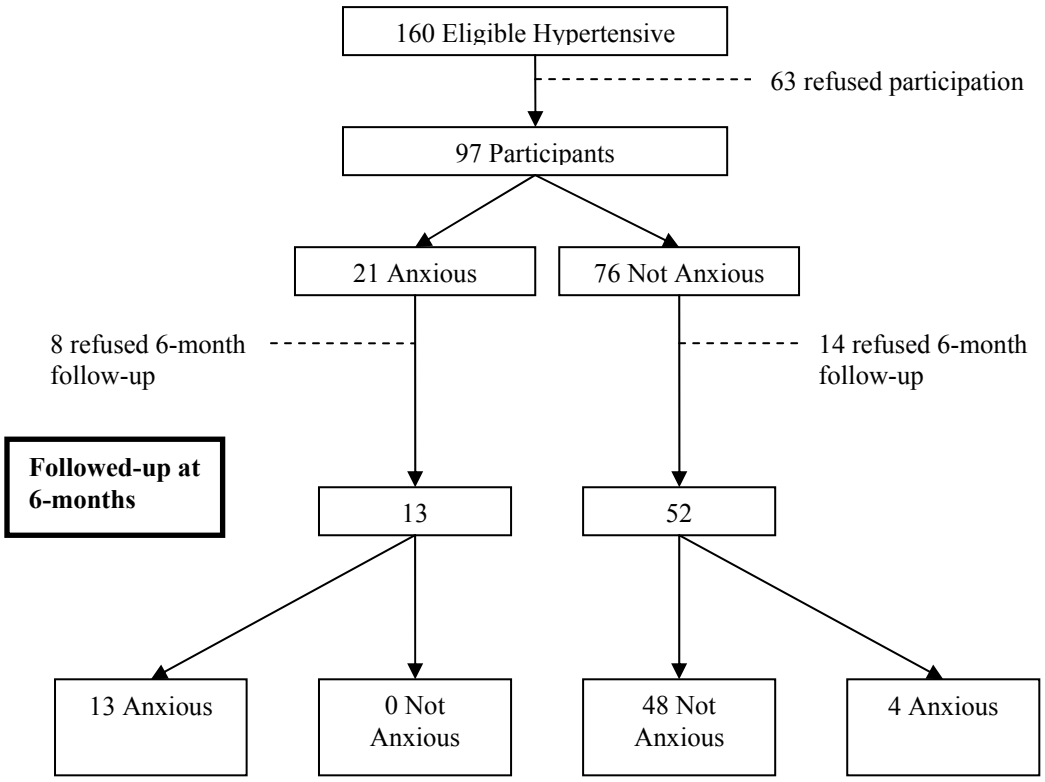
Figure 3.5: Persistence of state anxiety over the first six-month follow-up in patients with hypertension



3.1.8.4 Trait anxiety in hypertensive patients

The persistence of trait anxiety in hypertensive patients over the initial six-month follow-up is depicted in Figure 3.6. The mean (SD) trait anxiety score at baseline was 33.3 (11.4), with 21 (21.6%) patients reporting high levels of trait anxiety (STAI-T scores $\geq$ 40). The STAI-T was returned and completed at six-months by 67 (69.1%) patients; the mean (SD) score was 32.6 (11.2). Of these patients, high levels of trait anxiety were present at follow-up in 17 (25.4%) individuals. Of the hypertensive patients reporting high levels of trait anxiety at baseline, 52.6% continued to report high levels at six-months.

Figure 3.6: Persistence of trait anxiety over the first six-month follow-up in patients with hypertension



### 3.1.9 Six-month outcomes measures

#### 3.1.9.1 Quality of life in AF patients

The mean (SD) quality of life score at baseline was 20.4 (5.7). The Dartmouth COOP charts were completed and returned at six-months by 71 (70.3%) patients; the mean (SD) score was 20.2 (6.2). Table 3.10 summarises the correlation coefficients of baseline demographic, clinical, and psychological variables with quality of life at six-month follow-up. Of the variables entered, gender, ethnicity, employment status, total and dichotomised BDI score ($< 10$ and $\geq 10$), total and dichotomised state and trait anxiety scores ($< 40$ and $\geq 40$) all correlated significantly with quality life at six-months. Significant variables were then entered into a stepwise regression model. When both the continuous and dichotomous representation of a variable were significant, the continuous version was entered into the model. As shown in Table 3.11, baseline BDI score afforded the best independent predictor of six-month QoL in patients with AF, with gender and current employment status also predicting. The full model accounted for 34% of the variance in QoL at six-months.

Table 3.10: Correlation between baseline demographic, clinical and psychological characteristics and quality of life scores at six months in AF patients (n=70)

| | Correlation with quality of life scores at six months | Significance (p) |
|---|---|---|
| *Demographic characteristics* | | |
| **Age** (years) | 0.12 | 0.17 |
| **Gender** | -0.35 | **0.01** |
| **Ethnicity** | -0.27 | **0.01** |
| **Employment status** | 0.23 | **0.03** |
| **Deprivation score** (based on postcode) | 0.11 | 0.18 |
| *Clinical characteristics* | | |
| **Type of AF** | -0.01 | 0.48 |
| **Duration of AF** | -0.02 | 0.45 |
| *Psychological characteristics* | | |
| **Total BDI score** | 0.47 | **<0.001** |
| **BDI scores above and below cut-off** (dichotomised <10 or ≥10) | 0.33 | **<0.001** |
| **Total state anxiety score** | 0.42 | **<0.001** |
| **State anxiety scores above and below cut-off** (dichotomised <40 or ≥40) | 0.31 | **0.001** |
| **Total trait anxiety score** | 0.41 | **<0.001** |
| **Trait anxiety scores above and below cut-off** (dichotomised <40 or ≥40) | 0.38 | **0.005** |

Table 3.11: Independent baseline predictors of six month quality of life (stepwise linear regression model) in AF patients

| Model | Contribution to $R^2$ | B | Beta | 95% CI for B | F | Significance (p) |
|---|---|---|---|---|---|---|
| 1. BDI | 0.20 | 0.41 | 0.46 | 0.22 - 0.60 | 18.90 | **<0.001** |
| 2. BDI | 0.29 | 0.38 | 0.43 | 0.20 - 0.56 | | |
| Gender | | -3.88 | -0.31 | -6.42- -1.34 | 15.22 | **<0.001** |
| 3. BDI | 0.34 | 0.41 | 0.47 | 0.24 – 0.59 | 12.79 | **<0.001** |
| Gender | | -3.40 | -0.27 | -5.90 - -0.92 | | |
| Employment | | 3.22 | 0.24 | 0.55 – 5.90 | | |

#### 3.1.9.2 Mortality and MACE in AF patients

No deaths occurred during the initial six-month follow-up in patients with AF, with only one MACE being reported (transient ischaemic attack (TIA)).

#### 3.1.9.3 Quality of life in hypertensive patients

The mean (SD) quality of life score at baseline was 19.9 (5.3). The Dartmouth COOP charts were completed and returned at six-months by 68 (70.1%) patients, with a mean (SD) score of 20.5 (6.2). Table 3.12 summarises the correlation coefficients of baseline demographic, clinical, and psychological variables with quality of life at six-month follow-up. Of the variables entered, employment status, total and dichotomised BDI score ($< 10$ and $\geq 10$), total and dichotomised state and trait anxiety scores ($< 40$ and $\geq 40$) all correlated significantly with quality life at six-months. Significant variables were again entered into a stepwise regression model. As before, when both the continuous and dichotomous representation of a variable were significant, the continuous version was entered into the model. As shown in Table 3.13, baseline BDI score afforded the best independent predictor of six-month QoL in patients with hypertension, with current employment status also being entered into the model. The total model accounted for 18% of the variance in QoL at six-months.

Table 3.12: Correlation between baseline demographic and psychological characteristics and quality of life scores at six months in hypertensive patients (n=65)

| | Correlation with quality of life scores at six months | Significance (p) |
|---|---|---|
| *Demographic characteristics* | | |
| **Age** (years) | 0.06 | 0.31 |
| **Gender** | -0.14 | 0.13 |
| **Ethnicity** | -0.12 | 0.17 |
| **Employment status** | 0.27 | **0.02** |
| **Deprivation score** (based on postcode) | 0.10 | 0.22 |
| *Psychological characteristics* | | |
| **Total BDI score** | 0.35 | **<0.01** |
| **BDI scores above and below cut-off** (dichotomised <10 or ≥10) | 0.27 | **0.02** |
| **Total state anxiety score** | 0.30 | **<0.01** |
| **State anxiety scores above and below cut-off** (dichotomised <40 or ≥40) | 0.30 | **<0.01** |
| **Total trait anxiety score** | 0.34 | **<0.01** |
| **Trait anxiety scores above and below cut-off** (dichotomised <40 or ≥40) | 0.36 | **<0.01** |

Table 3.13: Independent baseline predictors of six month quality of life (stepwise linear regression model) in hypertensive patients

| Model | Contribution to $R^2$ | B | Beta | 95% CI for B | F | Significance (p) |
|---|---|---|---|---|---|---|
| 1. BDI | 0.11 | 0.32 | 0.35 | 0.11 – 0.53 | 9.00 | **<0.01** |
| 2. BDI | 0.18 | 0.34 | 0.37 | 0.13 – 0.54 | 8.15 | **0.01** |
| Employment | | 3.84 | 0.29 | 0.83 – 6.84 | | |

3.1.9.4 Mortality and MACE in hypertensive patients

One death occurred during the first six-months of follow-up among the hypertensive patients, with two individuals being admitted for a MACE (TIA, MI/CABG).

### 3.1.10 Summary of main findings

- AF and hypertensive patients displayed similar levels of depression, state anxiety, and QoL.
- AF patients displayed higher levels of trait anxiety than patients with hypertension.
- No significant differences in any of the psychological parameters were observed between PAF and permanent AF patients.
- Depression and anxiety (state and trait) were common co-morbid conditions in both AF and hypertensive patients.
- Significant symptoms of depression (BDI score $\geq$ 10) persisted at six-months in approximately 50% of patients at six-months (52.6% vs. 48.3% for AF and hypertensive patients, respectively).
- BDI score afforded the best independent predictor of six-month QoL in patients with AF and hypertension, with gender and current employment status also being entered into the model for patients with AF.

## 3.2 Stress study

### 3.2.1 Baseline characteristics of participants

The demographic and clinical characteristics of the participants, 14 AF patients, 10 hypertensive patients, and 10 healthy individuals are summarised in Table 3.14. All three groups were comparable in terms of age, ethnicity, occupational status, and body mass index (BMI). Clinically, with the exception of warfarin, no significant differences in co-morbidity and medication usage were observed between the AF and hypertensive patients.

### 3.2.2 Mental stress

#### 3.2.2.1 Haemodynamic reactivity

The haemodynamic reactivity to mental stress in the euhydrated state is summarised in Table 3.15 and Figures 3.7 to 3.10. Four time points X three participant group MANOVAs revealed temporal effects for all haemodynamic variables: systolic blood pressure (SBP), $F$ (3,93) = 36.36, p<.001, $\eta^2$ = .54, diastolic blood pressure (DBP), $F$ (3,93) = 23.40, p<.001, $\eta^2$ = .43, mean arterial pressure (MAP), $F$ (3,93) = 31.85, p<.001, $\eta^2$ = .51, and heart rate (HR), $F$ (3,93) = 42.30, p<.001, $\eta^2$ = .58. Post-hoc analyses showed that SBP, DBP, MAP, and HR were elevated following the stress task (p<.05), with only SBP and HR returning to baseline levels at 30 and 60-minutes recovery. Time X participant group interactions demonstrated that no significant differences in the temporal response to stress emerged for the three participant groups

Table 3.14: Baseline demographic and clinical characteristics of the AF and hypertensive patients and healthy individuals

| | **AF patients** (n = 14) | **Hypertensive patients** (n = 10) | **Healthy controls** (n = 10) | ***F*** | $x^2$ | ***P*** |
|---|---|---|---|---|---|---|
| *Demographic characteristics, n (%)* | | | | | | |
| **Mean (SD) age,** Years | 67.4 (6.1) | 66.9 (5.0) | 63.2 (4.3) | 1.99 | | 0.15 |
| **Ethnicity,** N, (%) | | | | | | |
| Caucasian | 14 (100.0) | 10 (100.0) | 8 (80.0) | | 5.10 | 0.27 |
| Afro-Caribbean | 0 (0.0) | 0 (0.0) | 1 (10.0) | | | |
| South-Asian | 0 (0.0) | 0 (0.0) | 1 (10.0) | | | |
| **Mean (SD) BMI,** $Kg/M^2$ | 27.1 (4.0) | 28.0 (3.8) | 24.4 (3.3) | 2.38 | | 0.11 |
| *Clinical characteristics, n (%)* | | | | | | |
| **Hypertension** | 14 (100.0) | 10.0 (100.0) | | | | |
| **Myocardial Infarction** | 2 (14.3) | 1 (10.0) | | | 0.00 | 1.00 |
| **Coronary artery disease** | 3 (21.4) | 2 (20.0) | | | 0.00 | 1.00 |
| **Stroke** | 3 (21.4) | 1 (10.0) | | | 0.03 | 0.84 |
| **Transient Ischemic Attack** | 1 (7.1) | 0 (0.0) | | | 0.00 | 1.00 |
| *Current Medication, n (%)* | | | | | | |
| **Warfarin** | 11 (78.6) | 0 (0.0) | | | 11.51 | <**0.01** |
| **Antiplatelet** | 4 (28.6) | 5 (50.0) | | | 0.41 | 0.52 |
| **Digoxin** | 3 (21.4) | 0 (0.0) | | | 0.88 | 0.35 |
| **Diuretics** | 8 (57.1) | 2 (20.0) | | | 1.96 | 0.16 |
| **Beta-Blocker** | 6 (42.9) | 1 (10.0) | | | 1.67 | 0.20 |
| **Calcium Channel Blockers** | 7 (50.0) | 6 (60.0) | | | 0.00 | 0.95 |
| **Angiotensin-converting-enzyme (ACE) inhibitor** | 4 (28.6) | 6 (60.0) | | | 1.25 | 0.26 |
| **Angiotensin-II-receptor blocker** | 5 (35.7) | 0 (0.0) | | | 2.61 | 0.11 |
| **Statin** | 9 (64.3) | 8 (80.0) | | | 0.14 | 0.70 |

### 3.2.2.2 Rheological reactivity

Table 3.16 displays the rheological reactivity to mental stress in the euhydrated state. MANOVA yielded a significant temporal effect for haematocrit (Hct), $F$ (3,93) = 3.10,

$p<0.05$, $\eta^2 = .09$, with levels increasing during the stress task ($p<.05$) and returning back to baseline levels at 30 and 60-minutes recovery. Although no significant time X participant interaction effect was observed, $F$ (6,93) = 1.73, $p = .14$, $\eta^2 = .10$, further analysis demonstrated that the AF patients were the only group to demonstrated a significant rise (1.6%) during the stress task.

Table 3.15: Mean (SD) haemodynamic response to mental stress in a euhydrated state

| | **AF Patients (n = 14)** | **Hypertensive Patients (n = 10)** | **Healthy Controls (n = 10)** |
|---|---|---|---|
| SBP (mmHg) | | | |
| *Baseline (1)* | 133.7 (18.2) | 144.7 (8.9) | 120.8 (12.5) |
| *Task (2)* | 150.0 (18.7)* | 160.5 (11.3)* | 141.4 (10.7)* |
| *30-min recovery (3)* | 139.8 (18.1)** | 149.0 (11.3)** | 124.1 (18.0)** |
| *60-min recovery (4)* | 140.4 (19.2)** | 149.9 (13.8) | 123.7 (19.6)** |
| DBP (mmHg) | | | |
| *Baseline (1)* | 78.6 (7.4) | 80.3 (8.5) | 74.9 (7.2) |
| *Task (2)* | 86.4 (9.4)* | 86.9 (10.1)* | 84.2 (5.6)* |
| *30-min recovery (3)* | 82.7 (9.6) | 85.5 (11.7) | 77.9 (7.5)** |
| *60-min recovery (4)* | 84.5 (9.9)* | 84.0 (11.3) | 78.0 (8.7)** |
| MAP (mmHg) | | | |
| *Baseline (1)* | 99.8 (11.4) | 104.1 (9.5)§ | 91.3 (10.5) |
| *Task (2)* | 108.7 (12.0)* | 116.0 (10.1)* | 105.3 (10.8)* |
| *30-min recovery (3)* | 104.1 (9.3) | 109.9 (11.7)§ | 95.8 (11.7)** |
| *60-min recovery (4)* | 106.8 (14.5) | 109.7 (11.6)§ | 94.4 (12.3)** |
| HR (Beats/min) | | | |
| *Baseline (1)* | 65.9 (13.1) | 56.1 (5.4) | 53.2 (5.5)† |
| *Task (2)* | 74.0 (15.1)* | 64.7 (6.0)* | 62.8 (10.5)* |
| *30-min recovery (3)* | 63.9 (13.4)** | 59.3 (6.0) | 53.6 (5.0)† |
| *60-min recovery (4)* | 63.8 (13.4)** | 57.3 (5.6)** | 52.2 (5.0)† |

* Significantly different from baseline ($p<.05$)
** Significantly different from task ($p<.05$)
† Significantly different from AF patients ($p<.05$)

Figure 3.7: Systolic blood pressure response to mental stress in a euhydrated state

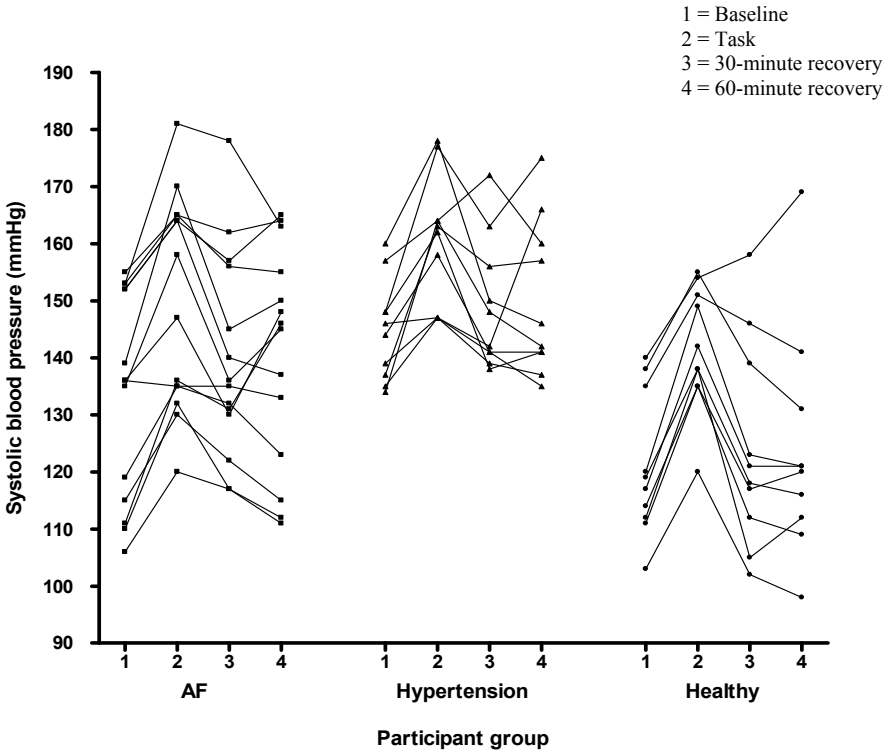



Figure 3.8: Diastolic blood pressure response to mental stress in a euhydrated state

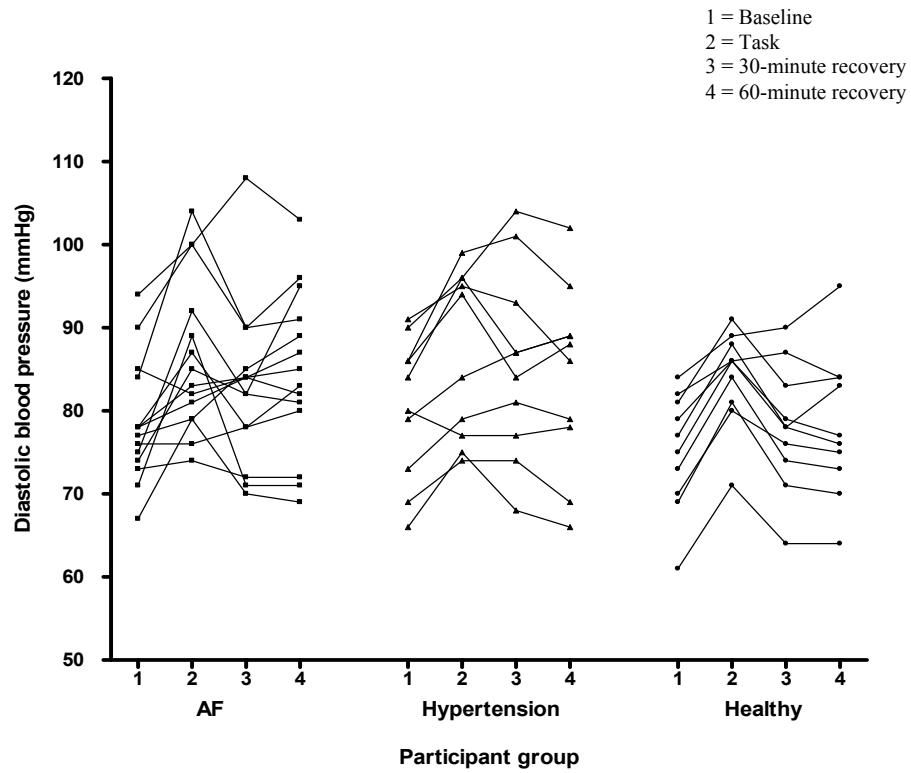


Figure 3.9: Mean arterial blood pressure response to mental stress in a euhydrated state

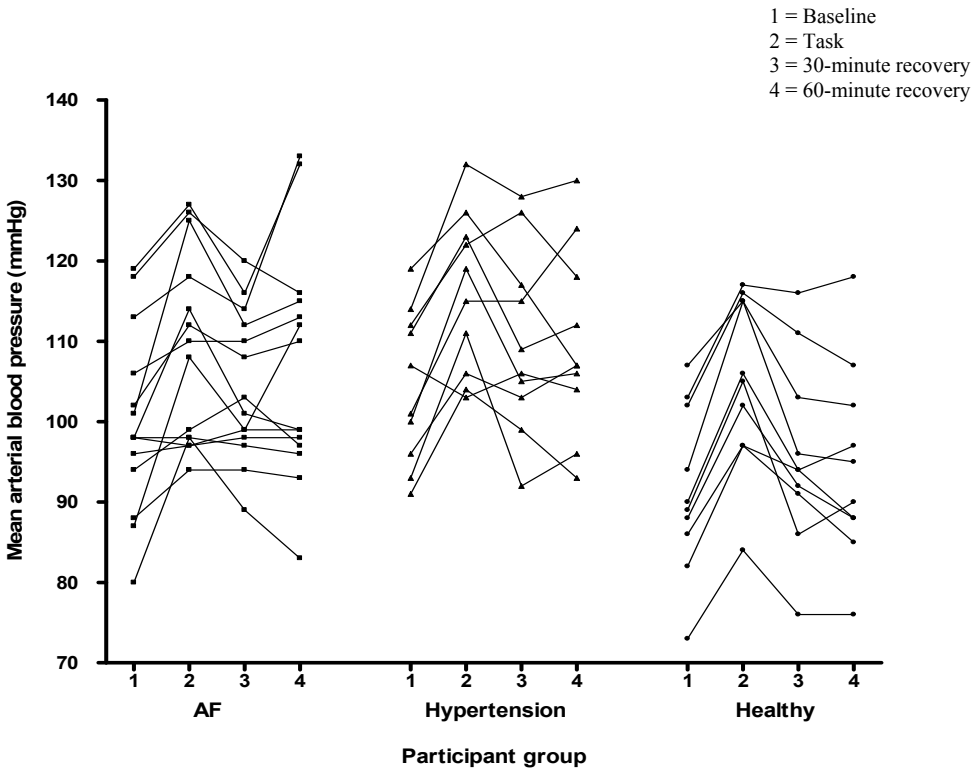



Figure 3.10: Heart rate response to mental stress in a euhydrated state

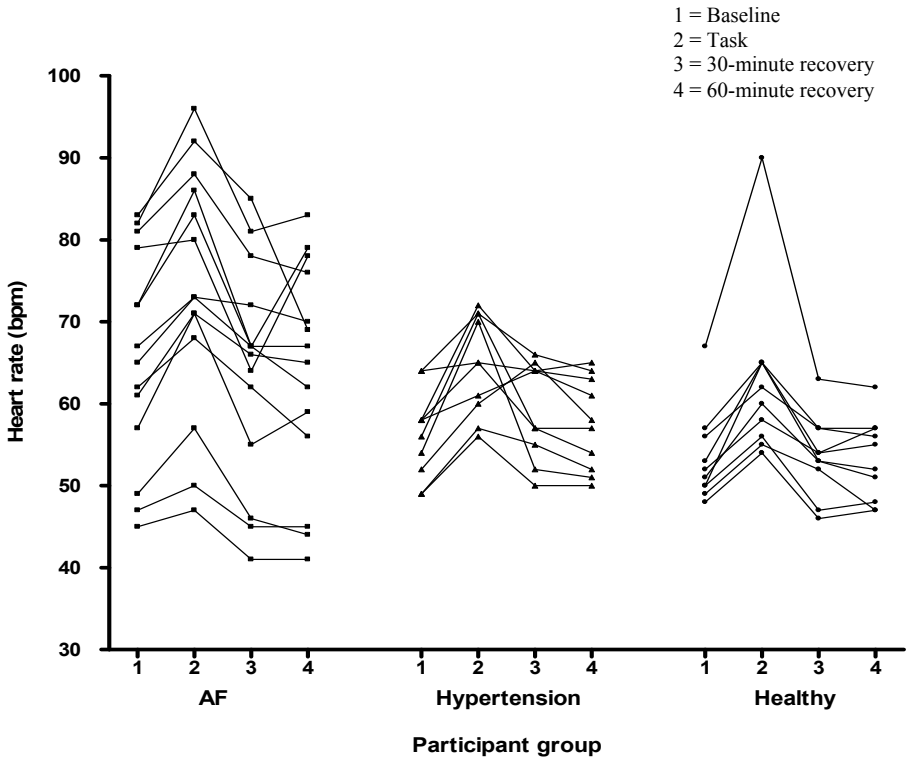


Table 3.16: Mean (SD) haematocrit response to mental stress in a euhydrated state

| | **AF Patients (n = 14)** | **Hypertensive Patients (n = 10)** | **Healthy Controls (n = 10)** |
|---|---|---|---|
| Hct (%) | | | |
| *Baseline (1)* | 39.9 (4.6) | 42.2 (2.5) | 38.6 (3.6) |
| *Task (2)* | 41.5 (3.9)* | 42.1 (2.6) | 39.4 (3.3) |
| *30-min recovery (3)* | 40.7 (4.7) | 41.9 (2.3) | 39.6 (3.4) |
| *60-min recovery (4)* | 40.6 (5.0) | 42.3 (3.0) | 39.6 (3.2) |

* Significantly different from baseline ($p<.05$)

### 3.2.2.3 Endothelial reactivity

A summary of the endothelial reactivity to mental stress in the euhydrated state is illustrated in Table 3.17. Although MANOVAs showed no temporal effects for von Willebrand Factor (vWF), $F$ (3,93) = 2.38, p = .09, $\eta^2$ = .07, and soluble E-selectin (sE-sel), $F$ (3,93) = 2.85, p = .07, $\eta^2$ = .08, there was a trend for vWF levels to increase during the task in all three participant groups. Statistical adjustment for mental stress-induced haemoconcentration attenuated the increase in vWF levels observed in AF patients and healthy controls. Time X participant group interactions demonstrated that no significant differences in the temporal response to stress emerged for the three participant groups.

Table 3.17: Endothelial response to mental stress in a euhydrated state

| | AF Patients (n = 14) | Hypertensive Patients (n = 10) | Healthy Controls (n = 10) |
|---|---|---|---|
| Mean (SD) vWF (U/l) | | | |
| *Baseline (1)* | 132.4 (20.9) | 130.9 (12.0) | 125.5 (25.7) |
| *Task (2)* | 135.0 (15.4) | 134.3 (19.1) | 128.3 (21.4) |
| *30-min recovery (3)* | 132.9 (23.4) | 125.3 (17.9) | 118.6 (17.7) |
| *60-min recovery (4)* | 130.0 (17.9) | 133.9 (19.9) | 118.4 (15.3) |
| Median (IQR) sE-sel (ng/ml) | | | |
| *Baseline (1)* | 30.0 (11.6 – 66.3) | 36.8 (15.5 – 63.1) | 40.0 (32.8 – 55.0) |
| *Task (2)* | 27.0 (11.0 – 63.1) | 36.8 (17.0 – 63.1) | 37.5 (30.3 – 55.0) |
| *30-min recovery (3)* | 26.0 (11.1 – 52.6) | 37.0 (19.1 – 67.5) | 33.5 (29.8 – 53.1) |
| *60-min recovery (4)* | 33.0 (11.1 – 52.6) | 36.0 (18.3 – 65.9) | 47.5 (33.8 – 60.8) |

### 3.2.2.4 Platelet reactivity

The platelet reactivity to mental stress in the euhydrated state is reported in Table 3.18. MANOVAs revealed no temporal effect for platelet count (Plt), $F$ (3,90) = .05, p = .93, $\eta^2$ = .00, mean platelet mass (MPM), $F$ (3,90) = .60, p = .54, $\eta^2$ = .02, platelet P-selectin (pP-sel), $F$ (3,90) = 1.03, p = .36, $\eta^2$ = .03, and platelet adhesion (% bound platelets), $F$ (2,54) = 1.33, p = .26, $\eta^2$ = .05. Significant effects were observed for mean platelet volume (MPV), $F$ (3,93) = 11.58, p<.001, $\eta^2$ = .27, and soluble P-selectin (sP-sel), $F$ (3,93) = 5.36, p<.01, $\eta^2$ = .15. Post-hoc analysis revealed a significant increase in MPV during the stress task (p<.05), with levels returning back to baseline levels 30 minutes into the recovery period. Subsequent analysis for sP-sel found that the temporal effect for sP-sel was driven by elevated levels at 60-minute recovery compared to baseline (p<.05). Time X participant group interactions demonstrated that no significant differences in the temporal response to stress emerged for the three participant groups.

Table 3.18: Platelet response to mental stress in a euhydrated state

| | **AF Patients (n = 14)** | **Hypertensive Patients (n = 10)** | **Healthy Controls (n = 10)** |
|---|---|---|---|
| Mean (SD) Plt ($10^3$/µl) | | | |
| *Baseline (1)* | 198.2 (83.7) | 201.5 (50.3) | 229.9 (40.8) |
| *Task (2)* | 203.4 (82.9) | 198.1 (42.1) | 228.2 (47.2) |
| *30-min recovery (3)* | 201.5 (84.3) | 187.4 (38.5) | 236.0 (47.3) |
| *60-min recovery (4)* | 189.9 (55.0) | 199.5 (39.6) | 237.7 (47.2) |
| Mean (SD) MPV (f/l) | | | |
| *Baseline (1)* | 7.3 (0.5) | 7.2 (0.8) | 7.0 (0.5) |
| *Task (2)* | 7.8 (0.8)* | 7.7 (0.8)* | 7.4 (0.6)* |
| *30-min recovery (3)* | 7.3 (0.8) | 7.2 (0.6) | 7.1 (0.7) |
| *60-min recovery (4)* | 7.6 (0.7) | 7.4 (0.7) | 7.3 (0.5) |
| Mean (SD) MPM (pg) | | | |
| *Baseline (1)* | 1.83 (0.1) | 1.81 (0.3) | 1.78 (0.1) |
| *Task (2)* | 1.86 (0.1) | 1.85 (0.3) | 1.77 (0.2) |
| *30-min recovery (3)* | 1.85 (0.2) | 1.85 (0.3) | 1.75 (0.2) |
| *60-min recovery (4)* | 1.83 (0.1) | 1.89 (0.4) | 1.78 (0.2) |
| Median (IQR) sP-sel (ng/ml) | | | |
| *Baseline (1)* | 155.0 (103.8 – 207.5) | 157.7 (98.8 – 215.0) | 100.0 (78.8 – 142.5) |
| *Task (2)* | 137.5 (98.8 – 192.8) | 137.0 (100.0 – 188.8) | 105.0 (83.8 – 156.3) |
| *30-min recovery (3)* | 147.5 (103.8 – 196.3) | 152.2 (103.8 – 257.5) | 105.0 (95.0 – 150.0) |
| *60-min recovery (4)* | 147.5 (123.8 – 212.5) | 170.0 (112.5 – 257.7) | 107.5 (93.8 – 151.3) |
| Median (IQR) pP-sel (ng/ml) | | | |
| *Baseline (1)* | 1150.0 (710.0 – 1385.0) | 1105.0 (1000.0 – 1750.0) | 1310.0 (1072.5 – 1587.5) |
| *Task (2)* | 1050.0 (780.0 – 1150.0) | 1030.0 (840.0 – 1362.5) | 1400 (600.0 – 1485.0) |
| *30-min recovery (3)* | 1150.0 (900.0 – 1385.0) | 715.0 (530.0 – 930.0) | 1080.0 (727.5 – 1710.0) |
| *60-min recovery (4)* | 1300.0 (950.0 – 1475.0) | 880.0 (605.0 – 1285.0) | 1325.0 (850.0 – 1837.5) |

* Significantly different from baseline ($p<.05$)

### 3.2.3 Postural stress

#### 3.2.3.1 Haemodynamic reactivity

Table 3.19 summarises the haemodynamic perturbation to postural stress in the euhydrated state. MANOVAs revealed temporal effects for DBP, $F$ (3,84) = 4.82, $p<.01$, $\eta^2 = .14$, and HR, $F$ (3,81) = 19.41, $p<.001$, $\eta^2 = .42$, although no significant effects for SBP, $F$ (3,84) = 1.93, $p = .17$, $\eta^2 = .06$, and MAP, $F$ (3,84) = 1.96, $p = .13$, $\eta^2 = 0.7$ were evident. Post-hoc analysis revealed a significant increase in HR from baseline to task ($p<.05$) which returned to baseline levels at 30 and 60-minutes recovery. Subsequent analysis for DBP indicated that the temporal effect was driven by the elevated levels at 30 and 60-minute recovery compared to baseline ($p<.05$). Time X participant group interactions demonstrated a significant effect for DBP, $F$ (6,84) = 3.46, $p<.01$, $\eta^2 = .20$, with only the hypertensive and healthy participants demonstrating a significant increase from baseline to task. No significant time X participant group interactions emerged for SBP, MAP, and HR.

#### 3.2.3.2 Rheological reactivity

Table 3.20 and Figure 3.11 present the analogous rheological data. MANOVA revealed a significant temporal effect for haematocrit (Hct), $F$ (3,93) = 46.6, $p<.001$, $\eta^2 = 0.60$. Post-hoc analysis indicated that there was a significant increase in Hct from baseline to task ($p<.05$) of approximately 2.5%, which returned to baseline levels at 30 and 60-minutes recovery. Time X participant group interactions demonstrated no significant differences in the temporal response to stress for the three participant groups.

Table 3.19: Mean (SD) haemodynamic response to postural stress in a euhydrated state

| | **AF Patients (n = 14)** | **Hypertensive Patients (n = 10)** | **Healthy Controls (n = 10)** |
|---|---|---|---|
| SBP (mmHg) | | | |
| *Baseline (1)* | 132.0 (18.4) | 139.6 (12.0)§ | 121.7 (13.8)‡ |
| *Task (2)* | 129.6 (21.2) | 139.3 (18.8)§ | 120.9 (14.5)‡ |
| *30-min recovery (3)* | 132.9 (15.2) | 144.7 (15.1)§ | 123.5 (17.2)‡ |
| *60-min recovery (4)* | 134.9 (13.8) | 143.3 (14.2)§ | 122.9 (16.4)‡ |
| DBP (mmHg) | | | |
| *Baseline (1)* | 78.6 (8.8) | 78.2 (9.5) | 75.9 (7.4) |
| *Task (2)* | 77.2 (10.9) | 82.2 (12.8) | 80.6 (8.0)* |
| *30-min recovery (3)* | 80.6 (9.3) | 83.7 (10.2)* | 77.1 (8.8) |
| *60-min recovery (4)* | 81.6 (8.6) | 83.3 (10.1) | 77.1 (8.9) |
| MAP (mmHg) | | | |
| *Baseline (1)* | 99.4 (12.5) | 101.3 (9.5) | 92.1 (10.1) |
| *Task (2)* | 96.6 (13.2) | 103.7 (13.3) | 94.6 (10.9) |
| *30-min recovery (3)* | 100.1 (11.1) | 107.0 (10.2) | 90.8 (15.9) |
| *60-min recovery (4)* | 103.1 (11.2) | 105.2 (8.1) | 93.3 (11.7) |
| HR (Beats/min) | | | |
| *Baseline (1)* | 65.7 (15.0) | 56.7 (6.5) † | 57.7 (6.7)† |
| *Task (2)* | 69.1 (17.2) | 63.2 (6.9)* | 64.9 (9.7)* |
| *30-min recovery (3)* | 66.8 (15.5) | 57.1 (6.7)** | 56.2 (5.5)† |
| *60-min recovery (4)* | 64.8 (14.1) | 55.0 (5.6)** | 55.8 (6.3) |

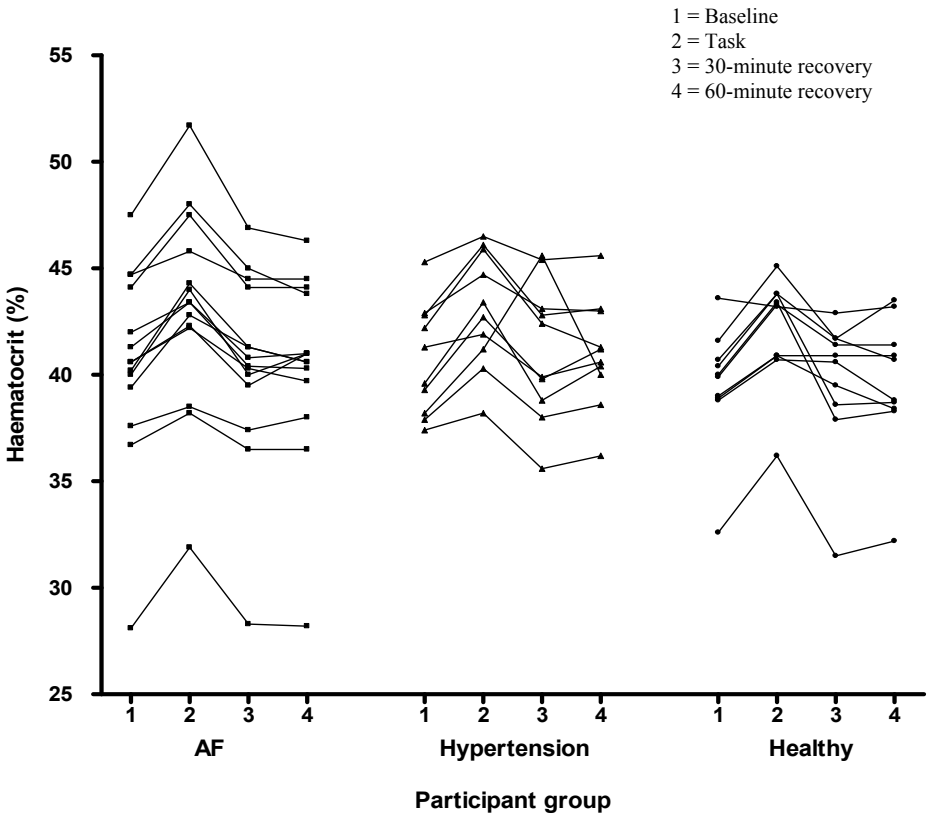
* Significantly different from baseline (p<.05)
** Significantly different from task (p<.05)
† Significantly different from AF patients (p<.05)

Table 3.20: Mean (SD) haematocrit response to postural stress in a euhydrated state

| | **AF Patients (n = 14)** | **Hypertensive Patients (n = 10)** | **Healthy Controls (n = 10)** |
|---|---|---|---|
| Hct (%) | | | |
| *Baseline (1)* | 40.5 (4.6) | 40.7 (2.6) | 39.6 (2.8) |
| *Task (2)* | 43.1 (3.9)* | 43.1 (2.8)* | 42.1 (2.6)* |
| *30-min recovery (3)* | 40.5 (4.5)** | 41.1 (3.3) | 39.7 (3.3) |
| *60-min recovery (4)* | 40.4 (4.4)** | 41.0 (2.6)** | 39.6 (3.2)** |

* Significantly different from baseline (p<.05)
** Significantly different from task (p<.05)

Figure 3.11: Mean haematocrit response to postural stress in a euhydrated state




3.2.3.3 Endothelial reactivity

The endothelial reactivity to postural stress in the euhydrated state is summarised in Table 3.21. MANOVAs revealed temporal effects for von Willebrand Factor (vWF), $F$ (3,93) = 3.92, p <.05, $\eta^2$ = .11, and soluble E-selectin (sE-sel), $F$ (3,93) = 9.16, p <.001, $\eta^2$ = .22. Although post-hoc analysis failed to demonstrate a significant increase in vWF during the task, there was a tendency toward an increase in patients with AF and hypertension. Post-hoc analysis indicated that levels of sE-sel increased during the task (p<.05), returning back to baseline levels at 30 and 60-minutes recovery. Interestingly, this increase appeared to be greater in patients with hypertension and healthy controls. The temporal effect for vWF remained when the raw data was adjusted for postural induced haemoconcentration, $F$ (3,93) = 6.87, p<.01, $\eta^2$ = .18, however, the effect for sE-sel, $F$ (3,93) = 2.31, p = .11, $\eta^2$ = .07, was no longer statistically significant. Time X

participant group interactions demonstrated no significant differences in the temporal response to stress for the three participant groups.

Table 3.21: Endothelial response to postural stress in a euhydrated state

| | **AF Patients (n = 14)** | **Hypertensive Patients (n = 10)** | **Healthy Controls (n = 10)** |
|---|---|---|---|
| Mean (SD) vWF (U/l) | | | |
| *Baseline (1)* | 127.4 (16.8) | 131.4 (25.0) | 123.6 (16.8) |
| *Task (2)* | 133.6 (13.6) | 144.8 (41.4) | 122.3 (15.6) |
| *30-min recovery (3)* | 125.2 (15.7) | 131.1 (22.9) | 119.3 (21.1) |
| *60-min recovery (4)* | 130.1 (15.4) | 133.9 (22.6) | 116.9 (21.3) |
| Median (IQR) sE-sel (ng/ml) | | | |
| *Baseline (1)* | 44.0 (15.0 – 67.8) | 37.0 (16.2 – 63.1) | 48.9 (36.3 – 115.0) |
| *Task (2)* | 50.8 * (18.8 – 67.8) | 48.0 * (15.4 – 67.8) | 56.0 (39.8 – 115.0) |
| *30-min recovery (3)* | 42.0 (14.8 – 67.8) | 29.0 (13.8 – 61.3) | 46.0 (33.5 – 68.8 ) |
| *60-min recovery (4)* | 45.5 (15.1 – 67.8) | 39.0 (20.4 – 67.0) | 46.5 (34.8 – 100.0) |

* Significantly different from baseline ($p<.05$)

### 3.2.3.4 Platelet reactivity

Table 3.22 presents the platelet reactivity to postural stress in the euhydrated state. MANOVAs yielded temporal effects for Plt, $F$ (3,93) = 4.36, $p<.05$, $\eta^2 = .12$, MPV, $F$ (3,90) = 7.75, $p<.001$, $\eta^2 = .21$, MPM, $F$ (3,81) = 4.27, $p<.05$, $\eta^2 = .14$, sP-sel, $F$ (3,93) = 4.98, $p<.05$, $\eta^2 = .14$, pP-sel, $F$ (3,93) = 3.19, $p<.05$, $\eta^2 = .09$, although no effect was observed for platelet adhesion (% bound platelets), $F$ (2,60) = .17, $p = .85$, $\eta^2 = .01$. Post-hoc analyses revealed significant increases in Plt, MPV, sP-sel during the stress task ($p<.05$), all of which returned back to baseline levels at 30 and 60-minutes recovery. pP-sel demonstrated a temporal decrease, which gained significance at 30 and 60-minutes recovery ($p<.05$). Time X participant group interactions demonstrated no

significant temporal differences between the three participant groups for any of the platelet variables. However, there was a trend, $F(2,31) = 1.73$, $p=.19$, for hypertensive patients to display a greater increase in sP-sel from baseline to task (32.5ng/ml) compared to AF patients (11.4 ng/ml) and healthy controls (7.5 ng/ml). Statistical adjustment for postural induced haemoconcentration attenuated the increase in sP-sel ($p>.05$), and transformed the significant increase in platelet count to a decrease ($<.05$).

Table 3.22: Platelet response to postural stress in a euhydrated state

| | **AF Patient (n = 14)** | **Hypertensive Patients (n = 10)** | **Healthy Controls (n = 10)** |
|---|---|---|---|
| Mean (SD) Plt ($10^3$/μl) | | | |
| *Baseline (1)* | 207.9 (80.9) | 195.5 (26.5) | 223.5 (33.8) |
| *Task (2)* | 228.2 (89.4)* | 204.3 (29.3) | 234.5 (50.7) |
| *30-min recovery (3)* | 213.5 (83.0)** | 194.0 (28.8) | 213.0 (55.0) |
| *60-min recovery (4)* | 217.2 (85.9) | 188.0 (21.6) | 214.2 (55.6) |
| Mean (SD) MPV (f/l) | | | |
| *Baseline (1)* | 7.6 (0.8) | 7.3 (1.0) | 6.9 (0.6) |
| *Task (2)* | 7.9 (1.0) | 7.7 (1.1) | 7.2 (0.5) |
| *30-min recovery (3)* | 7.5 (0.6) | 7.2 (1.0) | 6.6 (0.5)† |
| *60-min recovery (4)* | 7.5 (0.7) | 7.3 (0.9) | 6.8 (0.6) |
| Mean (SD) MPM (pg) | | | |
| *Baseline (1)* | 1.92 (0.2) | 1.84 (0.3) | 1.77 (0.2) |
| *Task (2)* | 1.91 (0.2) | 1.87 (0.3) | 1.80 (0.2) |
| *30-min recovery (3)* | 1.89 (0.2) | 1.78 (0.3) | 1.71 (0.1) |
| *60-min recovery (4)* | 1.91 (0.2) | 1.81 (0.3) | 1.66 (0.2) |
| Median (IQR) sP-sel (ng/ml) | | | |
| *Baseline (1)* | 147.5 (116.3 – 222.5) | 160.0 (118.8 – 280.0) | 107.5 (93.8 – 167.3) |
| *Task (2)* | 170.0 * (113.8 – 232.5) | 170.0 * (135.0 – 355.0) | 107.5 (93.8 – 186.3) |
| *30-min recovery (3)* | 140.0 (116.3 – 215.0) | 175.0 (117.5 – 230.0)** | 100.0 (90.0 – 173.8) |
| *60-min recovery (4)* | 140.0 ** (117.5 - 215.0) | 160.0 ** (108.8 – 251.3) | 107.5 (98.8 – 177.5) |
| Median (IQR) pP-sel (ng/ml) | | | |
| *Baseline (1)* | 1070.0 (430.0 – 1425.0) | 1010.0 (460.0 – 1105.0) | 1200.0 (985.0 - 1545.0) |
| *Task (2)* | 1020.0 (345.0 – 1450.0) | 1000.0 (460.0 – 1185.0) | 1140.0 (575.0 – 1767.0) |
| *30-min recovery (3)* | 950.0 (430.0 – 1157.0) | 860.0 (400.0 – 1080.0) | 930.0 ** (627.0 – 1362.5) |
| *60-min recovery (4)* | 770.0 (437.5 – 1132.5) | 620.0 (582.5 – 1080.0) | 1010.0 ** (632.5 – 1240.0) |

* Significantly different from baseline ($p<.05$)
** Significantly different from task ($p<.05$)
† Significantly different from AF patients ($p<.05$)

### 3.2.4 Effect of hydration status on the cardiovascular, rheological, and haemostatsic response to mental stress

Table 3.23 reports baseline haematocrit, total body water (TBW), intracellular water (ICW), and extracellular water (ECW) during the euhydrated and hyperhydrated sessions. Paired-samples t-tests revealed significantly elevated levels of TBW, $t(33) = 2.13$, $p < .05$, and ICW, $t(33) = 2.45$, $p < .05$ when participants attended in a hyperhydrated state, although ECW, $t(33) = 0.88$, $p = .38$, and haematocrit, $t(33) = 0.12$, $p = .90$ were not affected.

Table 3.23: Mean (SD) haematocrit and body impedance measures in the euhydrated and hyperhydrated conditions: mental stress sessions

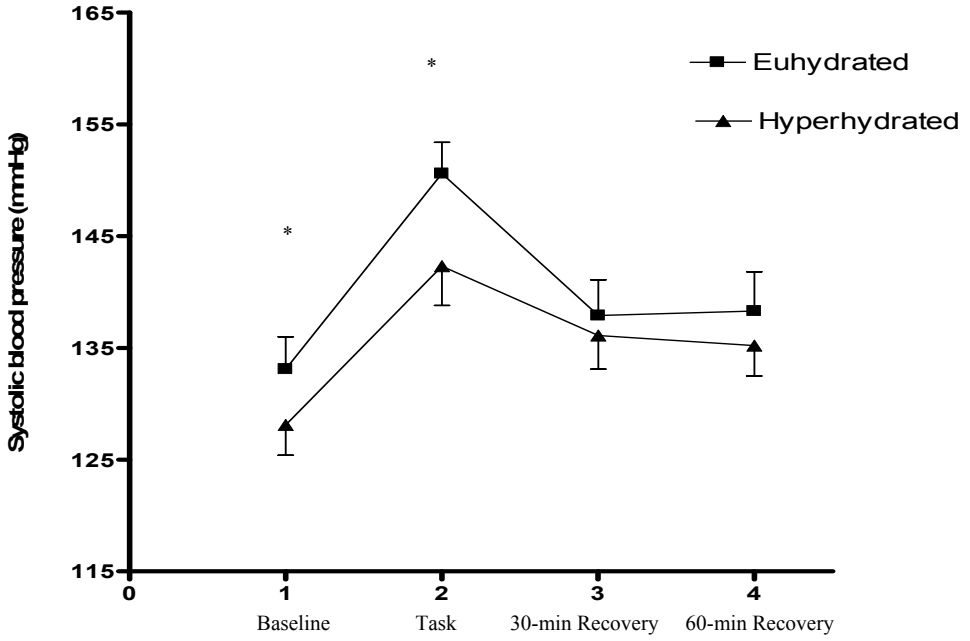
| Variable | Euhydration | Hyperhydration |
|---|---|---|
| Haematocrit (%) | 40.2 (4.0) | 40.1 (4.2) |
| Total body water (L) | 48.7 (6.5) | 49.4 (6.6)* |
| Intracellular water (L) | 28.7 (3.8) | 29.1 (3.8)* |
| Extracellular water (L) | 20.0 (3.1) | 20.2 (3.2) |

* Significantly different from euhydration condition

#### 3.2.4.1 Haemodynamic reactivity

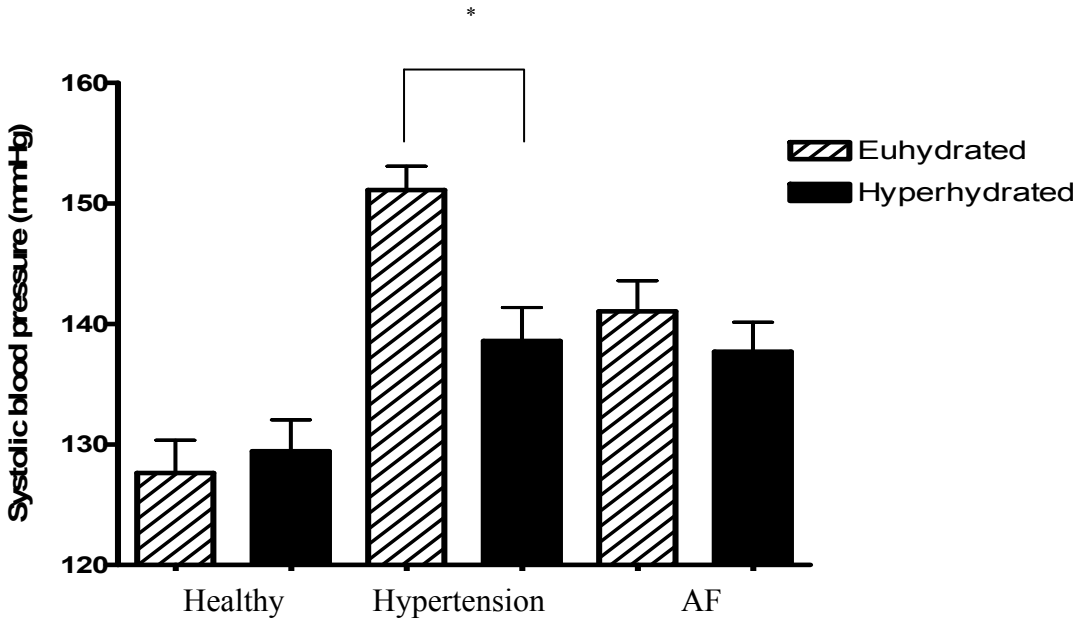
Condition X time point MANOVAs revealed a hydration condition effect for SBP, $F(1,31) = 5.48$, $p < .05$, $\eta^2 = .15$, DBP, $F(1,31) = 9.74$, $p < .01$, $\eta^2 = .24$, and MAP, $F(1,31) = 4.88$, $p < .05$, $\eta^2 = .14$ with levels being significantly lower during the stress task when participants were in a hyperhydrated state (Figures 3.12 and 3.13). A significant condition X participant group interaction effect emerged for SBP, $F(2,31) = 4.05$, $p<.05$, $\eta^2 = .21$ and MAP, $F(2,31) = 3.33$, $p < .05$, $\eta^2 = .18$, with hypertensive patients displaying the greatest reduction in arterial blood pressure (SBP and MAP) compared to patients with AF and healthy individuals (Figure 3.12a).

Figure 3.12: Mean (SEM) systolic blood pressure response to mental stress in a euhydrated and hyperhydrated state



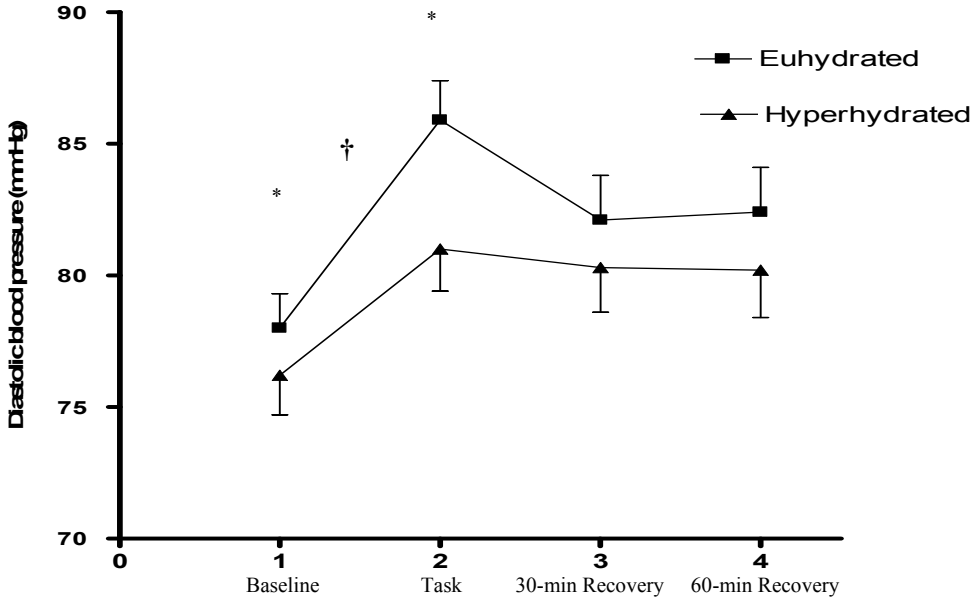

* Significantly different from hyperhydrated condition for given time point (p<.05)

Figure 3.12a: Mean (SEM) systolic blood pressure in a euhydrated and hyperhydrated state: effect of participant group




* Significant difference between hydration conditions (p<.01)

Figure 3.13: Mean (SEM) diastolic blood pressure response to mental stress in a euhydrated and hyperhydrated state




* Significantly different from hyperhydrated condition for given time point (p<.05)
† Significant difference in percentage change from baseline (1) to task (2) for two conditions

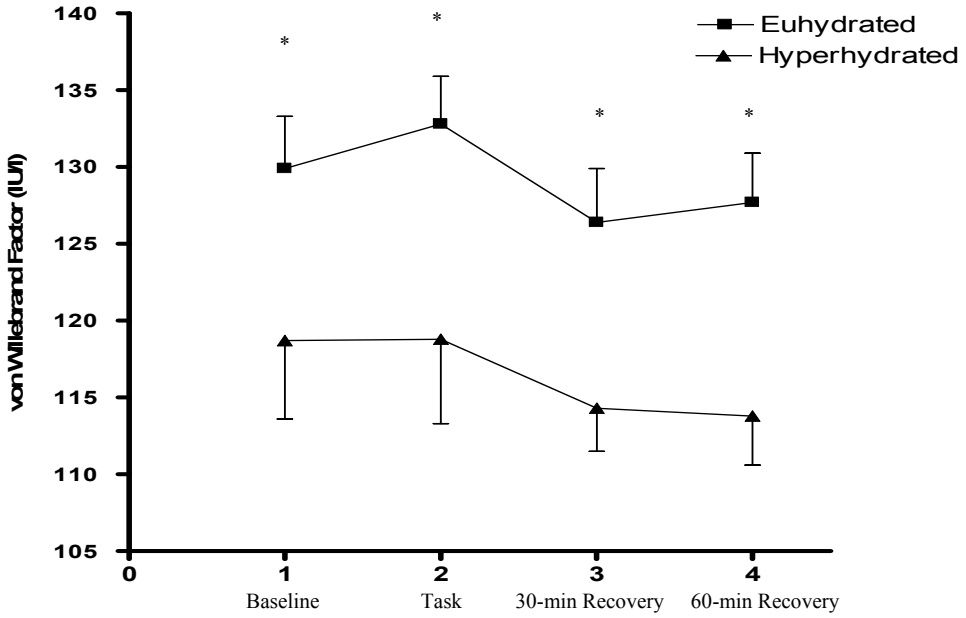
### 3.2.4.2 Rheological reactivity

No main effect for hydration was evident for haematocrit, $F$ (1,33) = .22, p = .65, $\eta^2$ = .01.

### 3.2.4.3 Endothelial reactivity

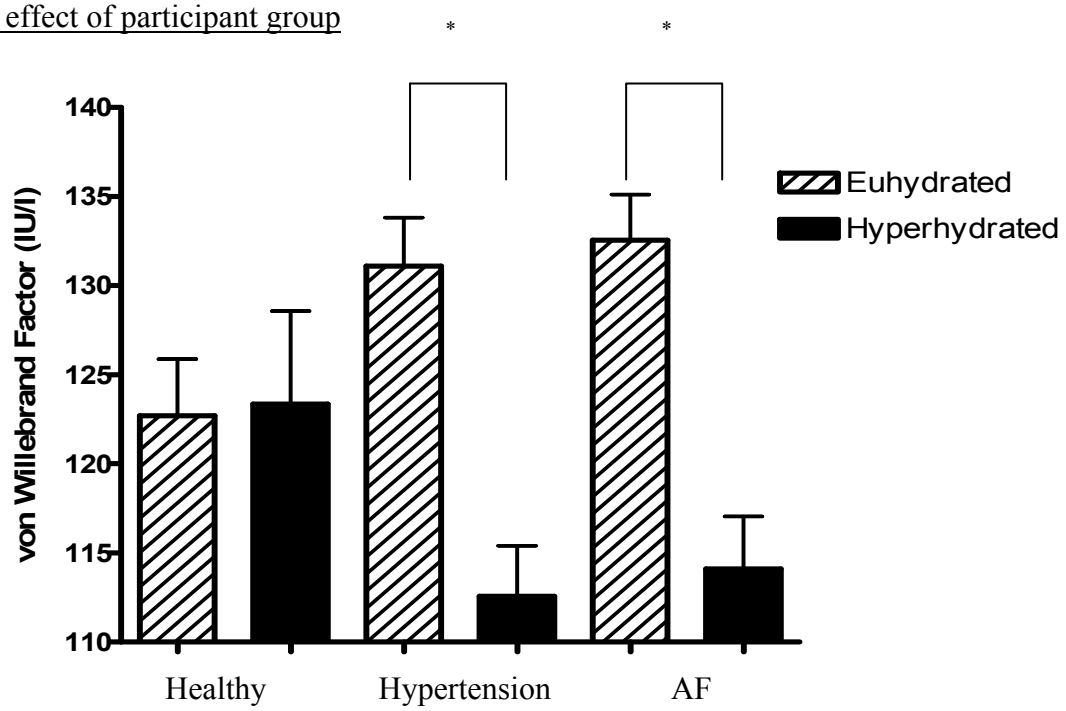
MANOVA revealed a condition effect for vWF, $F$ (1,31) = 11.04, p <.01, $\eta^2$ = .25, with levels being reduced at all measurement points when participants were hyperhydrated (Figure 3.14). There was a trend for differing effects of hydration between the three participant groups. Condition X participant groups interactions, $F$ (2,31) = 2.82, p=.08, $\eta^2$ = .15 (Figure 3.14a) demonstrated that patients with AF and hypertension displayed a reduction in vWF levels, with no significant change in healthy controls (Figure 3.14a).

Figure 3.14: Mean (SEM) von Willebrand Factor response to mental stress in a euhydrated and hyperhydrated state




* Significantly different from hyperhydrated condition for given time point (p<.05)

Figure 3.14a: Mean (SEM) von Willebrand Factor in a euhydrated and hyperhydrated state: effect of participant group

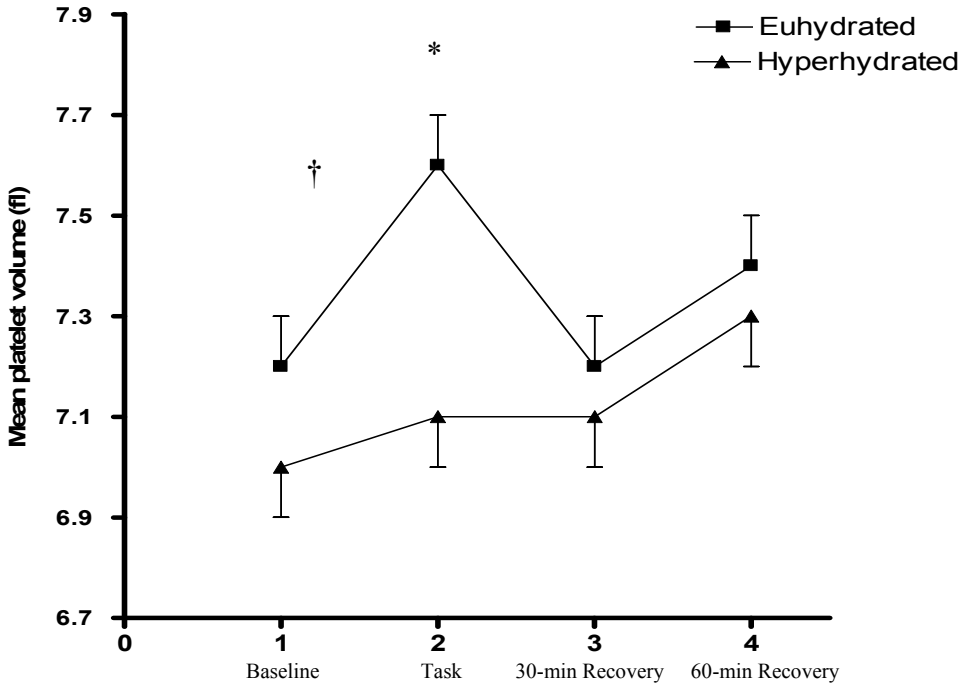



* Significant difference between hydration conditions (p<.01)

3.2.4.4 Platelet reactivity

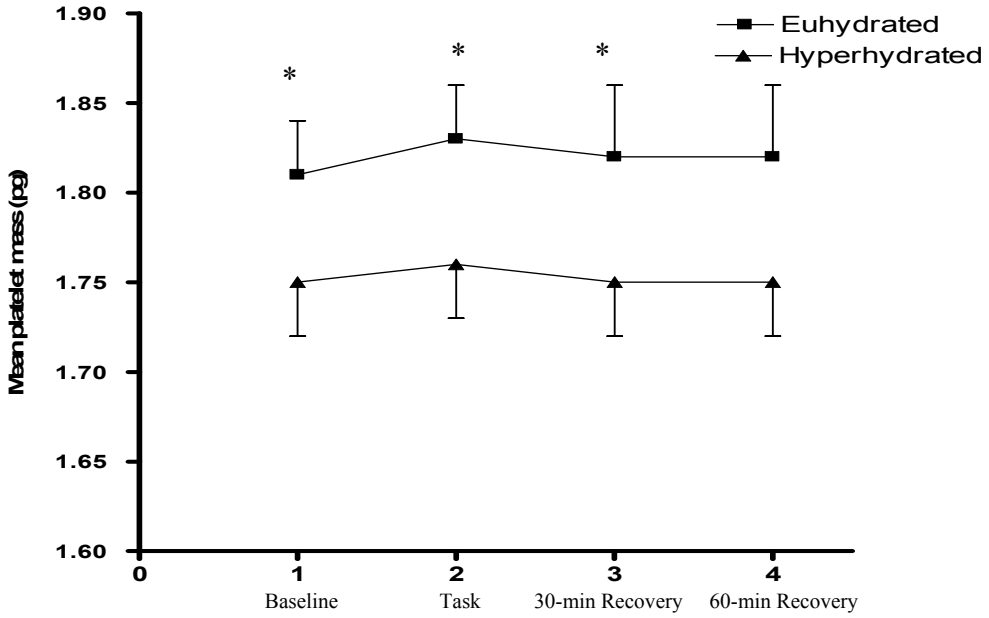
A summary of the platelet reactivity to mental stress in the two hydration conditions is depicted in Figures 3.15 to 3.17. MANOVA revealed condition effects for MPM, $F$ (1,27) = 7.91, p<.01, $\eta^2$ = .23, sP-sel (1,31) = 6.56, p<.05, $\eta^2$ = .18, and a trend for MPV, $F$ (1,28) = 3.16, p = .09, $\eta^2$ = .10. Post-hoc analyses revealed a significant reduction in baseline and task levels of MPM and MPV (p<.05), as well as an attenuation in the MPV response to the stress when participants were hyperhydrated (Figure 3.15). In addition, sPs-sel levels were significantly elevated at all measurement points when participants were hyperhydrated. No condition X participant group interaction effects emerged for any of the platelet variables.

Figure 3.15: Mean (SEM) platelet volume response to mental stress in a euhydrated and hyperhydrated state



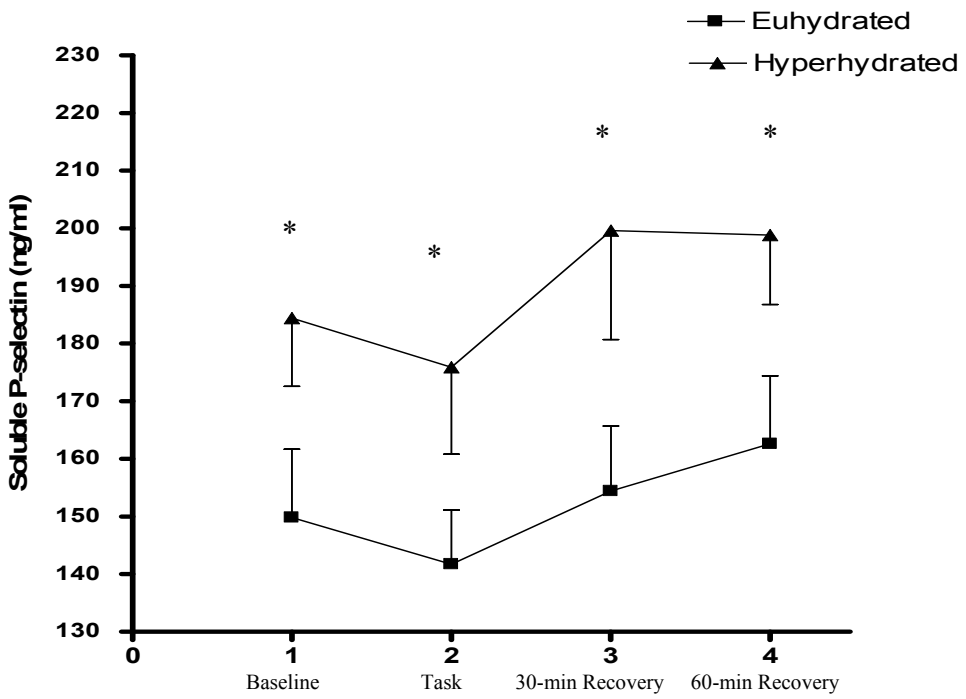

* Significantly different from hyperhydrated condition for given time point (p<.05)
† Significant different in percentage change from baseline (1) to task (2) for two conditions

Figure 3.16: Mean (SEM) platelet mass response to mental stress in a euhydrated and hyperhydrated state




* Significantly different from hyperhydrated condition for given time point ($p<.05$)

Figure 3.17: Mean (SEM) soluble P-selectin mass response to mental stress in a euhydrated and hyperhydrated state




* Significantly different from hyperhydrated condition for given time point ($p<.05$)

### 3.2.5 Effect of hydration status on the cardiovascular, rheological, and haemostatsic response to postural stress

Baseline haematocrit, TBW, ICW, and ECW for the euhydrated and hyperhydrated sessions are shown in Table 3.24. Paired-samples t-tests revealed no significantly differences in TBW, t (33) = 0.48, p = .64, ICW, t (33) = 0.70, p .49, ECW, t (33) = 0.79, p = .44, and haematocrit, t (33) = 1.56, p = .13.

Table 3.24: Mean (SD) haematocrit and body impedance measures in the euhydrated and hyperhydrated conditions: postural stress sessions

| Variable | Euhydration | Hyperhydration |
|---|---|---|
| Haematocrit (%) | 40.3 (3.6) | 39.6 (3.8) |
| Total body water (L) | 49.0 (6.8) | 49.4 (7.6) |
| Intracellular water (L) | 29.0 (4.1) | 29.6 (6.1) |
| Extracellular water (L) | 20.1 (3.1) | 19.9 (3.6) |

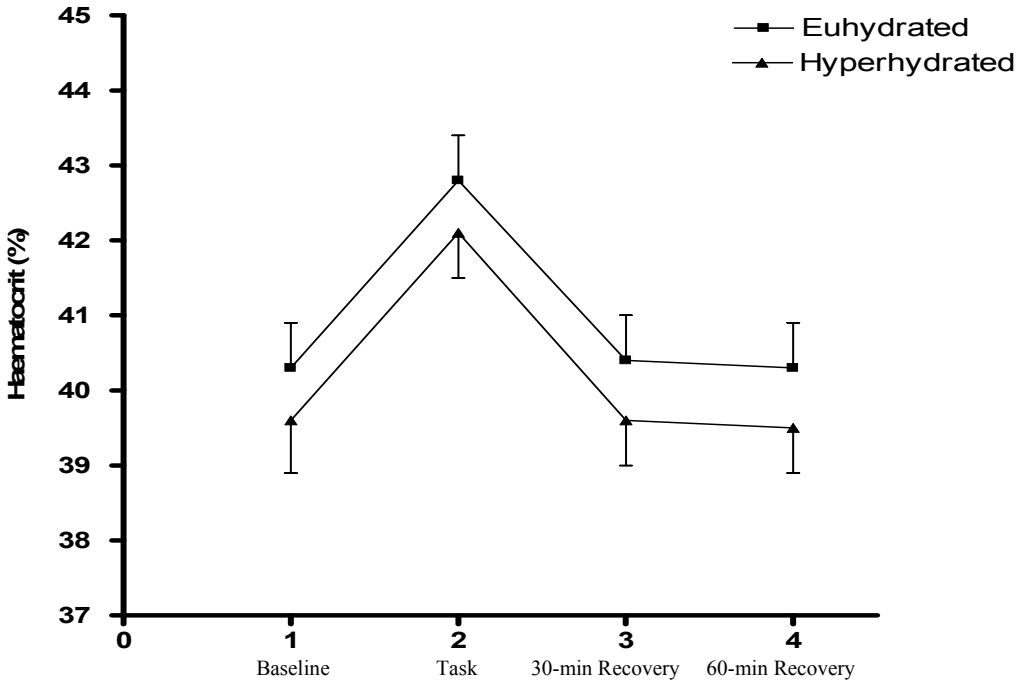
#### 3.2.5.1 Cardiovascular reactivity

There were no significant condition effects for any of the cardiovascular parameters: SBP, $F$ (1,29) = .23, p = .63, $\eta^2$ = .01, DBP, $F$ (1,29) = .02, p = .89, $\eta^2$ = .00, MAP, $F$ (1,29) = .06, p = .80, $\eta^2$ = .00, and HR, $F$ (1,27) = .50, p = .49, $\eta^2$ = .02.

#### 3.2.5.2 Rheological reactivity

The rheological reactivity to postural stress in the two hydration conditions is depicted in Figures 3.18. MANOVA revealed no significant effect condition for haematocrit, although there was a trend towards a lower level in a hyperhydrated state, $F$ (1,27) = 3.27, p = .08, $\eta^2$ = .11.

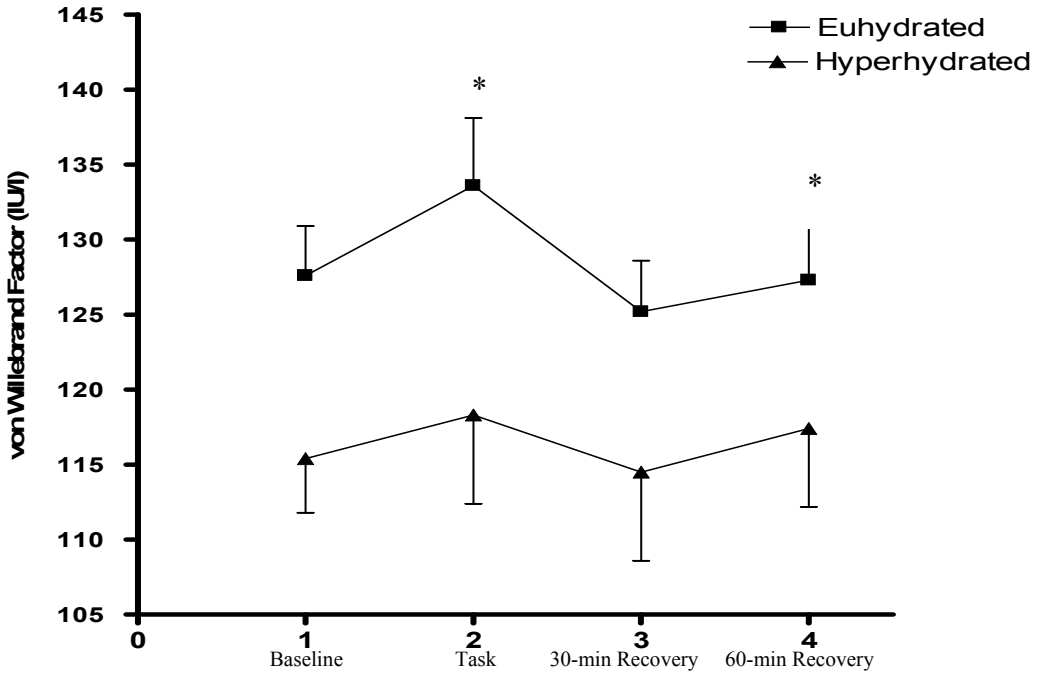
Figure 3.18: Mean (SEM) haematocrit response to postural stress in a euhydrated and hyperhydrated state




3.2.5.3 Endothelial reactivity

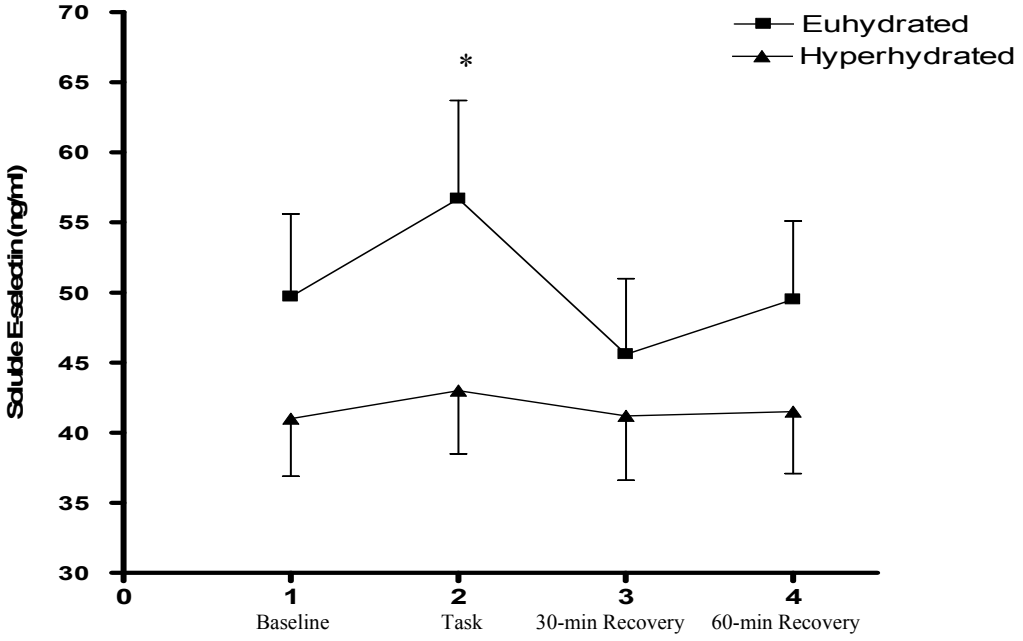
A summary of the endothelial reactivity to postural stress in the two hydration conditions is presented in Figures 3.19 and 3.20. MANOVAs revealed a significant condition effect for vWF, $F$ (1,31) = 5.25, p <.05, $\eta^2$ = .15, and sE-sel, $F$ (1,31) = 5.42, p <.05, $\eta^2$ = .15. Post-hoc analyses indicated that hyperhydration not only reduced vWF and sEs-sel levels, but attenuated their reactivity to postural stress. Condition X participant group analysis revealed that healthy individuals displayed a significant decrease in sE-sel levels when hyperhydrated, with AF and hypertensive patients displaying no significant change, $F$ (2,31) = 4.89, p<.05, $\eta^2$ = .24 (Figure 3.20a).

Figure 3.19: Mean (SEM) von Willebrand Factor response to postural stress in a euhydrated and hyperhydrated state



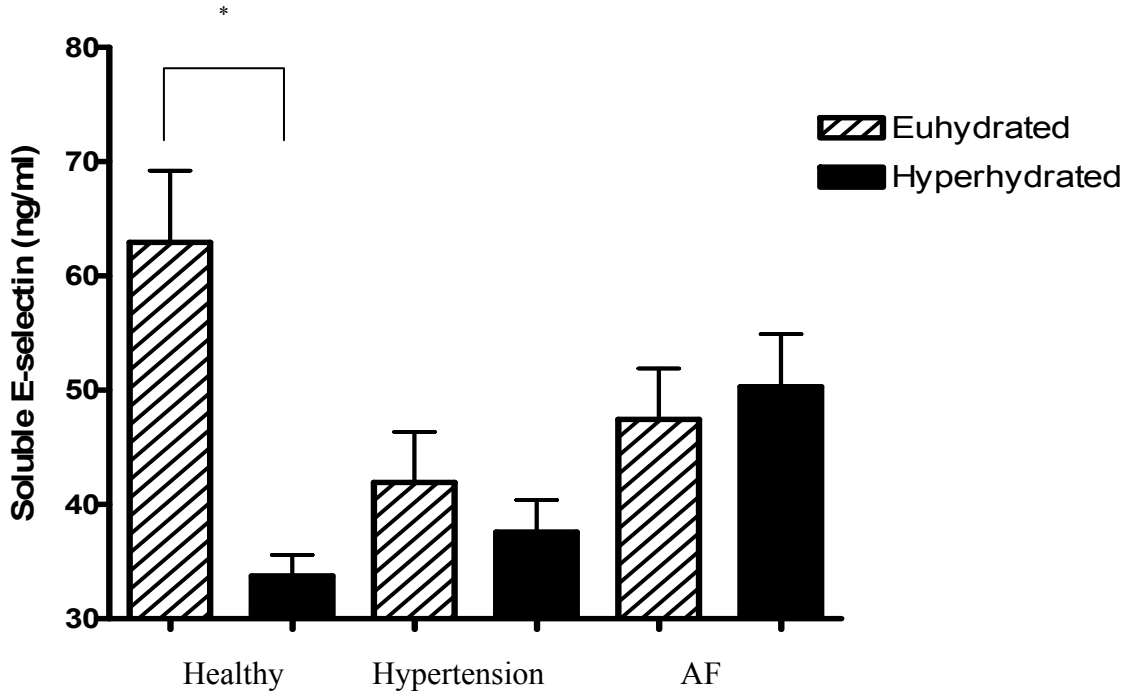

* Significantly different from hyperhydrated condition for given time point ($p<.05$)

Figure 3.20: Mean (SEM) soluble E-selectin response to postural stress in a euhydrated and hyperhydrated state




* Significantly different from hyperhydrated condition for given time point ($p<.05$)

Figure 3.20a: Mean (SEM) soluble E-selectin levels in a euhydrated and hyperhydrated state: effect of participant group

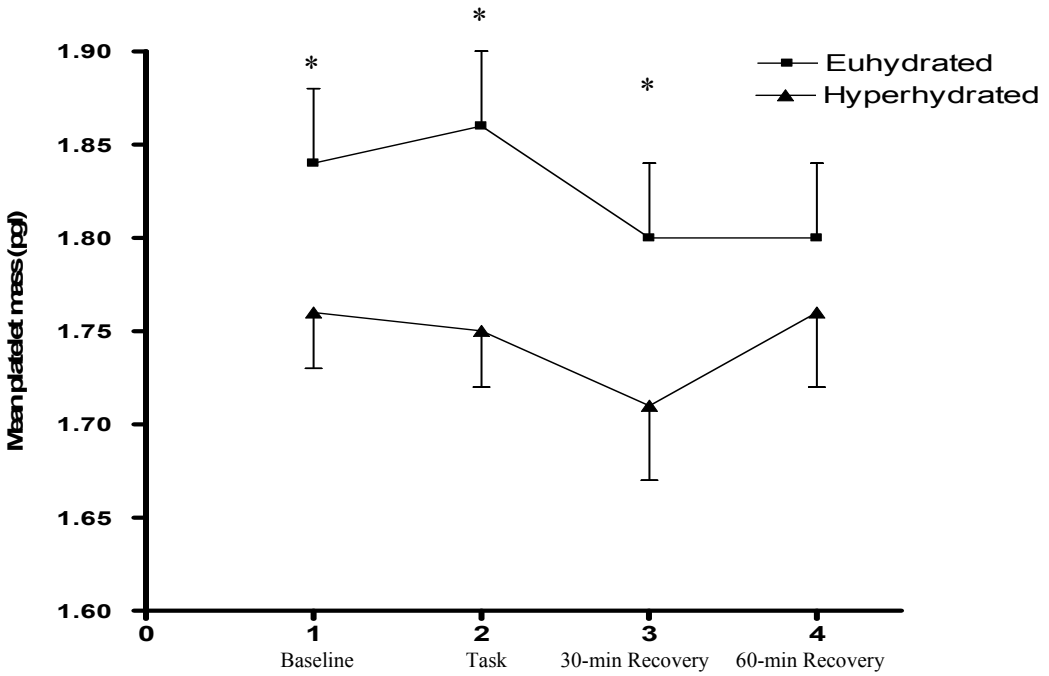



* Significant difference between hydration conditions ($p<.01$)

3.2.5.4 Platelet reactivity

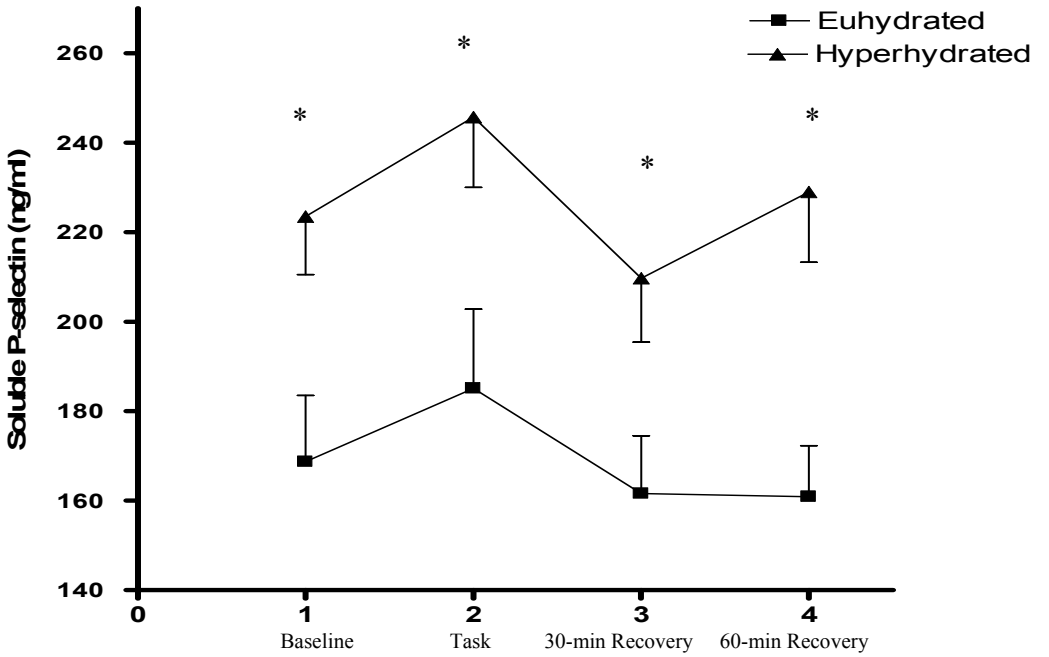
Platelet reactivity to postural stress in the two hydration conditions is depicted in Figures 3.21 to 3.23. MANOVA revealed significant condition effects for MPM, $F$ (1,26) = 4.36, $p<.05$, $\eta^2 = .11$, sP-sel (1,31) = 16.95, $p<.001$, $\eta^2 = .35$, and pP-sel, $F$ (1,31) = 25.91, $p<.001$, $\eta^2 = .46$. Post-hoc analyses revealed that baseline and task MPM levels were lower when participants were hyperhydrated, with levels of sP-sel and pP-sel being higher during hyperhydartion ($p<.05$). No condition X participant group interaction effects emerged for any of the platelet variables.

Figure 3.21: Mean (SEM) platelet mass response to postural stress in a euhydrated and hyperhydrated state



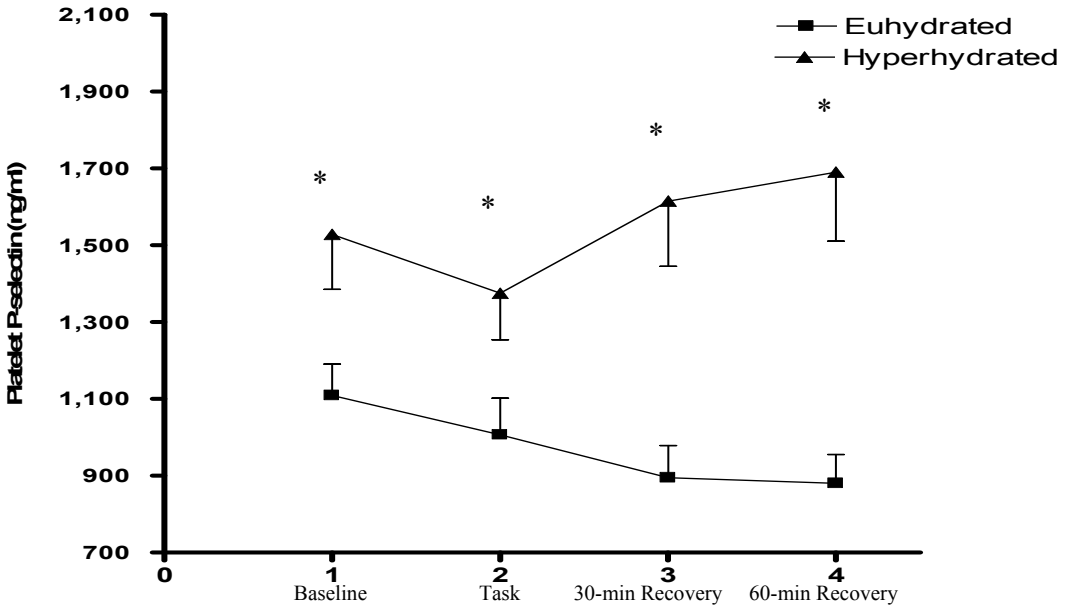

* Significantly different from hyperhydrated condition for given time point ($p<.05$)

Figure 3.22: Mean (SEM) soluble P-selectin response to postural stress in a euhydrated and hyperhydrated state




* Significantly different from hyperhydrated condition for given time point ($p<.05$)

Figure 3.23: Mean (SEM) platelet P-selectin response to postural stress in a euhydrated and hyperhydrated state




* Significantly different from hyperhydrated condition for given time point ($p<.05$)

### 3.2.6 Summary of main findings

#### 3.2.6.1 Mental stress

- Mental stress elicited significant increases in all haemodynamic variables (SBP, DBP, MAP, HR). The SBP response to the stress task was more pronounced in healthy controls compared to patients with AF and hypertension. Hyperhydration significantly lowered baseline and task SBP and DBP levels, as well as attenuating the DBP response to the stress task. Interestingly, the reduction in SBP with hyperhydration was only apparent in patients with hypertension.
- A significant haemoconcentration was observed following the stress task, although this response was only significant in patients with AF (1.6% increase in

Hct). No significant effect of hydration was evident for stress-induced haemoconcentration.

- Although non-significant, there was a trend for vWF to increase following the stress task. Hyperhydration significantly lowered vWF levels at all measurement points, although this was only evident in the patients with AF and hypertension.
- Mental stress yielded a significant increase in MPV from baseline to task. Hyperhydration significantly lowered baseline and task MPM and MPV levels, in addition to abolishing the MPV response to the stress task. sP-sel and pP-sel levels were significantly elevated at all measurement points when participants were hyperhydrated.

3.2.6.2 Postural stress

- Postural stress yielded a significant increase in HR in all three participant groups, whereas the increase in DBP was only evident in hypertensive patients and healthy controls.
- Postural stress elicited a significant haemoconcentration, with Hct increasing by approximately 2.5%. There was a tendency for hyperhydration to lower Hct levels across all measurement points.
- Perturbation of the endothelium was apparent following postural stress. sE-sel increased from baseline to task across all participant groups, with a trend towards an increase in vWF levels being observed in patients with AF and hypertension. Hyperhydration reduced vWF and sE-sel levels as well as

attenuating the sE-sel response to postural stress in patients with hypertension and healthy controls.

- Significant increases in platelet count, MPV, MPM, sP-sel were observed following the postural stress task. pP-sel demonstrated a temporal decrease, which was significant at 30 and 60-minute recovery. Platelet count response was exaggerated in AF patients, whereas hypertensive patients demonstrated the greatest increase in sP-sel from baseline to task. Hyperhydration significantly reduced MPM levels at baseline and task, as well as elevating levels of sP-sel and pP-sel.

# CHAPTER 4

## Discussion

### 4.1 Questionnaire study

The prevalence and prognostic significance of depression has received a large amount of attention in patients with coronary heart disease (CHD). Such exploration in AF patients has not been forthcoming, and the current study is the first to examine the persistence of depression and anxiety, and their implications for disease progression and future QoL.

The current study revealed that significant symptoms of depression (BDI scores >10) were evident in 38% of patients with AF at baseline, with elevated state and trait anxiety (STAI score ≥40) being reported in 28% and 38% of patients, respectively. Depression and anxiety (trait) were found to be highly common co-morbid conditions in AF patients, with 71% of patients reporting BDI scores ≥10 also exhibiting high levels of anxiety. Rates of depression in patients following a MI range from 20 to 37% [47,48,50,51,58,67,68], with two meta-analyses demonstrating that depressive symptoms yield a two-fold elevation in all-cause mortality, cardiac mortality, and future cardiovascular events [76,77]. Anxiety is an additional negative emotion implicated in the progression of CHD. Similar prevalence rates of anxiety (24 – 31%) have been reported following a MI [67,79,80], although findings on its prognostic significance have been inconsistent [65-66,74,78-81]. Such findings imply that our cohort of AF patients present a comparable levels of psychological morbidity to post-MI patients. However, in contrast to previous research [50-51,67-68], elevated symptoms of depression were not more likely to be reported in females.

Hypertensive patients reported similar rates of depression (30%) and state anxiety (23%) to patients with AF, although hypertensive patients exhibited lower levels of trait anxiety (22%). Although no previously published data in AF patients exists, the prevalence of depression in hypertensive patients has received some attention [343 – 345]. Rabkin and colleagues are one of the few groups to explore this relationship, demonstrating that a diagnosis of major depression was three times more common among hypertensive patients even when known cardiac risk factors (age, sex, chronic co-morbidity, and current anti-hypertensive medication) were taken into account [344]. Bonnet and colleagues reported that the prevalence of mild depressive symptoms, measured by the Hospital Anxiety Depression scale were approximately 20% in hypertensive patients, with females displaying significantly higher levels than males (26% vs. 14%, respectively) [345].

In comparison to depression and anxiety, health-related quality of life (QoL) has been extensively studied in AF patients, with the current study revealing no significant differences in QoL between patients with AF and hypertension. Only five observational studies [107-111] have previously examined QoL in what could be termed a 'general' AF population, demonstrating that AF patients suffer a poorer QoL (SF-36) when compared to CHD patients [107], the general population [111], and healthy controls [107,109-110]. The largest (n = 152) observation study to date demonstrated that patients with PAF displayed QoL scores similar to cardiac disease patients (PTCA, MI, and heart failure) and significantly worse than healthy controls [107]. Nilsson and colleagues are the only authors to report differences in QoL between AF patients and a hypertensive control group [131]. In contrast to the current study, the authors demonstrated a lower QoL on six of the eight scales of the SF-36 in AF patients when

compared to hypertensive controls. However, it highly plausible that the differences between the two studies may be explained by the exaggerated baseline scores in the previous study, due to their highly symptomatic nature of their condition or experiencing the uncertainty of having to undergoing an invasive medical procedure (pulmonary vein isolation).

Differences in QoL between patients with PAF and permanent AF have not been subject to investigation. The current study, although not powered to detect differences between the sub-groups of AF patients, demonstrated that patients with PAF showed comparable levels of QoL when compared to patients with permanent AF ($t(93) = -1.28$; $p>.05$). Only one of the five observational studies examined QoL inclusively in a cohort of permanent AF patients. This study found that males with permanent AF displayed similar levels of QoL (SF-36) in comparison to an aged-matched control group in sinus rhythm [109]. The authors argued that having a predictable clinical course of rate control and anti-coagulation, in addition to relatively well-controlled heart rates, might explain the equivocal findings. However, a recent study demonstrated that there was no significant association between achieved heart rate either at rest or during exercise and QoL [346]. Conversely, the significant impairment in QoL reported in PAF patients [107-108,110] may be a consequence of rapid heart rates that are potentially more symptom-producing than permanent (rate-controlled) AF, or individuals perceiving their illness to be more intrusive on their everyday lives [347].

The current study reports that females AF patients have a poorer QoL than male AF patients ($t(99) = 3.43$; $p <.05$). Paquette and colleagues previously explored the potential gender differences in QoL in patients with PAF/persistent AF, demonstrating

that female patients display poorer physical component summary scores on the SF-36 than their male counterparts [108]. Although this result was confounded by the fact that female patients were significantly older than males, it was speculated that such discrepancies could not fully account for sex differences in QoL [108]. The authors argued that the greater impact of AF on QoL in women may be attributed to their heightened sensitivity to the disease and its associated symptoms, sex differences in the perception of illness, or a lower threshold for reporting illness burden. However, previous research has found that increased sensitivity to symptoms is unlikely to be a major factor driving these differences, as the impairment of QoL experienced by women persisted even after controlling for somatization scores [108].

No study to date has explored the course of depression and anxiety in patients with AF. Findings from the current study demonstrate that significant symptoms of depression (BDI scores $\geq$10) and trait anxiety (STAI scores $\geq$40), persisted over the first six-months of follow-up in 52.6% of patients. Such results add further support to our baseline data; AF patients experience a significant degree of psychological morbidity, which is protracted and not limited to a single point of observation.

The prognostic significance of depression and anxiety in predicting future QoL, MACE and mortality has not been studied in patients with AF. The current study demonstrates that female gender, ethnicity, employment status and baseline BDI, state and trait anxiety scores were significantly correlated with QoL at six-months. Stepwise regression analysis revealed that baseline BDI score provided the best independent predictor of QoL at follow-up. A study by Lane and colleagues examined the predictors of four and 12-month QoL in patients following MI [67,348]. At both time points,

baseline BDI, state and trait anxiety, male gender, and employment status were significantly correlated with QoL. Stepwise linear regression analysis demonstrated that baseline BDI score provided the best independent predictor of QoL, although living/partner status, Peel Index score, and state anxiety were also found to be of significance. The total model accounted for 23% and 28% of the variation in QoL scores at four and 12-months, respectively. Such findings are in line with previous research relating depressive symptomatology to future QoL in post-MI patients [64].

## 4.2 Stress study

The hypothesis that behavioural exposures such as physical activity, mental stress, and postural change can trigger the onset of acute coronary syndromes (ACS) is intuitively appealing. Although anecdotal [158-160] and epidemiological evidence [169] supports such a hypothesis, research examining the underlying mechanisms is far from conclusive. Controlled laboratory experiments have provided us with a useful model for examining the pathways through which such activities may precipitate ACS. The current study aimed to determine the effects of mental and postural stress on haemorheology, endothelial function, and markers of platelet reactivity in patients with AF. In addition, we examined whether an enhanced hydration status could attenuate the development of a prothrombotic state in response to such stressors.

### 4.2.1 Effect of stress and hydration status on haemodynamic reactivity

Mental stress elicited increases in SBP, DBP, MAP, and HR, whereas the postural stress only increased HR. The haemodynamic response to mental stress was not uniform across the three participant groups; healthy individuals demonstrated a trend toward exaggerated blood pressure reactivity (MAP) compared to patients with AF and

hypertension, $F$ (6,96) = 1.72, p = .13,η = .10. Overall, the magnitude of the haemodynamic reactions to mental stress [175-177,314,349-351] and the postural challenge [206,207,209,210,352-253] were broadly similar to those reported in previous studies. Previous research employing the PASAT as a laboratory stress task has been limited to healthy individuals [175-177,349-351], or on cardiac patients without a control group [314]. Although the current study was the first to use the PASAT to examine differences in reactivity between cardiac patients and healthy individuals, other studies, employing different stress tasks, have produced inconsistent findings [198-202,354].

Earlier studies have found that hypertensive patients display elevated haemodynamic reactivity in comparison to normotensive controls during acute behavioural stresses [355]. A recent study reiterated such findings, demonstrating an exaggerated blood pressure and heart rate response during mental stress in a hypertensive cohort [200]. Abstinence from medical therapy prior to the testing session may have accounted for the inconsistencies, with medication discontinued for only 12-hours prior to stress testing session in the current study in comparison to the four-week employed by Tomoda et al. [200]. Given that the wash out period for any given drug should exceed five times its half-life, it is clear that a 12-hour period of withdrawal would be insufficient for complete clearance, and may have lead to an attenuation of the haemodynamic response.

The current study demonstrates that hyperhydration reduced arterial blood pressure at rest, in addition to attenuating its responsiveness to the mental stress task. Interestingly, further analysis revealed that this reduction in blood pressure occurred mainly in

patients with hypertension. Studies examining the effect of acute water injection (~500 ml) have demonstrated a pressor response, characterised by an increase in total peripheral resistance and subsequently arterial blood pressure [356-360], which appeared to be maintained up to 50-minutes following fluid consumption [360-361]. Participants in the present study consumed their second bolus (500 ml) of fluid >90-minutes before baseline haemodynamic measures were obtained. This procedural nuance may explain the null effects observed in our healthy controls and AF patients. To our knowledge, the current study is the first to demonstrate a beneficial effect of fluid loading in a hypertensive cohort. Unfortunately, with a lack of objective measures of sympathetic activation, vascular compliance, naturetic peptide release, and renin/angiotensin II turnover it is difficult to speculate over potential mechanisms contributing to this improved blood pressure profile.

### 4.2.2 Effects of stress and hydration on haemorheological reactivity

A degree of haemoconcentration was observed following acute mental and postural stress, as revealed by a significant increase in haematocrit (Hct). The majority of previous research examining the haemorheological response to mental stress has been conducted on healthy individuals [175-183]. The magnitude of the increase seen in the healthy cohort, although not statistically significant, is of the same order as previously published research [175-183]. Data from patient populations are scarce, although Bacon and colleagues demonstrated that patients with coronary artery disease (CAD) displayed no significant changes in haematocrit or plasma viscosity following the PASAT [314].

The extent of haemoconcentration observed during mental stress was not uniform across the three participant groups; AF patients displayed an exaggerated response compared to healthy individuals, with hypertensive patients demonstrating no haemorheological change. Although the underlying mechanisms of mental stress-induced hemoconcentration remain to be fully elucidated, it is currently believed that increases in capillary pressure are the driving force behind this phenomenon [175-177,179,351]. If changes in hydrostatic pressure were the major determinant of transcapillary exchange one would expect relatively similar increases in Hct across all three participant groups, with healthy individuals potentially displaying a greater response due to their exaggerated haemodynamic reactivity. The lack of a haemorheological response observed in patients with hypertension could be attributed to elevated levels of arterial stiffness. It has been demonstrated that the chronic elevation of luminal pressure in hypertension can lead to increased collagen production, subsequently increasing intima-medial thickness and decreasing vessel compliance [362]. The progressive decrease in vascular compliance, which occurs predominately in central and conduit arteries, causes significant alterations in flow dynamics, decreasing microvascular perfusion [362] and potentially reducing transvascular exchange. The underlying hypertension observed in all our AF patients makes it unlikely that transferral of hydrostatic forces to the microcirculation is the sole explanation for differences between the three groups. It would appear plausible that AF patients exhibit greater capillary exchange as a result of increased vascular permeability. Small increases in permeability are considered to occur in a number of disease states, with inflammation being one of the main candidates for such changes [363]. Numerous studies have demonstrated that patients with AF display greater levels of inflammation in comparison to healthy controls measured through changes in plasma levels of IL-6

and CRP [364-365]. In light of such findings, it would appear reasonable to speculate that excessive capillary exchange in response to increases in hydrostatic pressure may be mediated by levels of microvascular inflammation.

Assumption of an upright posture leads to a rapid pooling of blood in the lower extremities, subsequently increasing gravitational hydrostatic pressure and causing shifts of plasma into the surrounding tissues [366-367]. The 2.5% increase in haematocrit or 13% decrease in plasma volume we observed following head-up-tilt (HUT) is consistent with previous research [205-213,215,217-225,368-369], and based on dye-dilution techniques translates to an approximately 350 – 400 ml loss of fluid into the interstitium [205-206,215,219,221]. This net movement of fluid is eventually halted when equilibrium is resumed due to increased interstial hydrostatic pressure and increased intravascular oncotic pressure [205]. The current study, in line with previous research [368-369], demonstrates that the restoration of plasma volume on resumption of supine position is complete within 30-minutes. In contrast to mental stress-induced haemoconcentration, no significant differences in the haemorheological response to posture were observed. We previously speculated that differences in the transferral of hydrostatic forces to the microcirculation, and inflammatory reductions in vascular permeability might influence transvascular shifts of plasma in response to such a stressor. During postural change, with capillary pressure in the lower limbs rising to approximately 100 mmHg [370], it would appear unlikely that the aforementioned variables would significantly influence this hydrostatically driven response.

### 4.2.2 Effects of stress and hydration on markers of endothelial dysfunction and platelet reactivity

Mental stress elicited a significant increase in MPV and a trend towards an increase in vWF levels, with postural change causing alterations in all indices of platelet reactivity and endothelial function. The increase in platelet count observed during postural stress was broadly similar to a previously reported result [211]. When examining the concentration of non-diffusible blood constituents' such as platelets, it is important to account for the volume in which they are measured. With the correction for plasma volume abolishing the changes we observed, it would appear that haemoconcentration is the mechanism underlying increases in platelet count in response to postural change. Other investigators have speculated that changes in platelet count and volume during postural stress may be due to increased splenic expulsion of platelets of increased size [213]. Although support for this hypothesis has been derived from catecholamine infusion studies [371-373], Cohn (1966) demonstrated that epinephrine not only produced arteriolar dilatation and venoconstriction but also elicited a loss of plasma volume [374].

Platelet size has been shown to reflect platelet activity [375], with changes in MPV thought to reflect the level of platelet stimulation (physiology) and/or the rate of platelet production (biology) [376]. Larger platelets have been shown to be denser [377], aggregate more rapidly, have a higher capacity for thromboxane $B_2$ production [378], release more serotonin and β-TG [379-380], and express more GP Ib and GP IIb-IIIa receptors [382-383]. As a consequence, larger platelets are considered to have a greater thrombotic potential [270]. Although the increase in MPV in response to mental stress was in contrast to previous research [203], the current study was the first to report an

increase in platelet size during postural change. Since such changes in platelet volume (MPV) cannot be accounted for by haemoconcentration or by alterations in spleen discharge, other physiological mechanisms need to be invoked. *In vitro* experiments by Jagroop and colleagues suggest MPV can be transiently increased by certain agonists [383]. These authors demonstrated that although epinephrine was unable to alter platelet volume on its own, when combined with stress related neurotransmitters (e.g. serotonin) it could be significantly increased. Such findings suggest that the change in MPV observed during the stress tasks may be due to an increase in size of existing platelets in the circulation rather than the expulsion of fresh platelets from the spleen.

Increased plasma levels and decreased intra-platelet levels of P-selectin further suggest that postural stress can cause an increase in platelet reactivity. Although previous research examining platelet activation in this respect is mainly limited to the assessment of platelet aggregation [211,213-214,216], Andrew and colleagues found no change in the platelet membrane expression of P-selectin using flow cytometry during standing [213]. The mechanisms responsible for increased P-selectin expression are initiated through an activation of the hypothalamic-pituitary-adrenocortical (HPA) axis and sympathetic-adrenal-medullary (SAM) system. The secreted catecholamines [209,210] are thought to bind to alpha-$_2$ adrenoreceptors on the platelet membrane [211] causing a translocation of intra-platelet α-granules [384]. When α-granules fuse with the platelet membrane there is a brief expression of P-selectin before it is proteolytically shed or actively cleaved from the cell surface. Although the current observations would appear to demonstrate this process, with haemoconcentration attenuating the increase in plasma levels of P-selectin other physiological mechanism cannot be discounted.

Although von Willebrand Factor (vWF) has consistently been shown to increase following acute mental stress [185-186,189,196], no study has assessed whether postural change can elicit changes in plasma indices of endothelial damage/dysfunction. Although there was a trend for vWF to increase during both stress tasks, with a significant increase in sE-sel during postural change, stress-induced haemoconcentration again appeared to account for such findings. With the hypertensive patients displaying no haemorheological change during mental stress it would appear plausible that any increase in vWF observed may be the result of shear stress [385] or catecholamine induced release from vascular endothelial cells [386].

With the exact mechanism responsible for transient increases in vWF yet to be fully determined [387], it is difficult to account for the reduction in vWF levels in patients with AF and hypertension. Although the most plausible explanation might be that an elevation in plasma volume would produce a subsequent dilution of the haemostatic molecule, no decrease in haematocrit levels was observed when participants were hyperhydrated. With increases in shear stress being implicated in the release of vWF, it may be expected that individuals displaying the greatest reduction in blood pressure when hyperhydrated would also display the greatest reduction in vWF levels. Although this appears to hold true for healthy individuals and patients with hypertension, such an explanation cannot account for the reduction in vWF levels in AF patients.

### 4.2.4 Clinical implications

Given the prognostic significance of depression and anxiety for CHD patients, it would appear that such variables could now be considered as novel risk factors for the development and progression of ACS. With the prevalence rates of depression and

anxiety observed in our AF cohort comparable to post-MI patients, it would appear they experience a significant degree psychological morbidity, which may be predictive future cardiovascular morbidity and mortality. Although the current study failed to demonstrate any predictive significance for depression and anxiety over a six-month follow-up period, it should be conceded that there were few events and power was insufficient to detect associations. It remains plausible that such relationships could emerge over more protracted follow-up periods with larger numbers of events. If this were the case, it may be beneficial to screen AF patients for psychological morbidities, providing effective and safe treatment strategies were appropriate.

The significant alteration in haemorheology, endothelial perturbation, and platelet reactivity observed during mental and postural stress provides further pathophysiological evidence for the behavioural triggering of ACS. It would be reasonable to assume that the haemoconcentration and increases in haemodynamic and mechanical shear stress could trigger plaque disruption. In addition, the increases in platelet morphology and reactivity would provide a prothrombotic milieu, which may transfer a disrupted plaque into a 'clinically active' plaque through partial or complete vessel occlusion. The exaggerated haemorheological reactivity observed during mental stress in AF patients may also predispose such individuals to a greater risk of plaque rupture and ACS during periods of emotional distress.

Although it has been previously demonstrated that increased fluid consumption is associated with a decreased risk of CHD [388], only speculative hypotheses have been provided to explain such findings. In an attempt to test the possibility that this is a causal association, the current study examined the effects of fluid loading on blood

rheology and haemostasis at rest and in response to commonly encountered behavioural activities. We demonstrated that a short term increase in hydration status has the potential to lower blood pressure in patients with hypertension, in addition to attenuating the haemodynamic reactivity to mental stress in all participant groups. Enhanced hydration was also shown to have significant benefits on endothelial function in patients with AF and hypertension. Although further prospective data are required to confirm such findings, our results would suggest that increased water consumption should be implemented into the 'package of care' for individuals with 'classical' risk factors for CHD.

### 4.2.5 Study limitations

A number of potential limitations need to be considered. Firstly, it could be argued that the lack of a control session reduces the strength of our study protocol. Although this may have merit, it has been consistently demonstrated that haematocrit does not change during a prolonged period of unstimulated rest [179-180,192]. Patterson and colleagues echoed these findings for the platelet proteins β-TG and PF-4 [192]; however, a recent study demonstrated a decrease in plasma P-selectin levels during 45 minute supine rest [389]. The likely decrease in P-selectin during sleep or prolonged supine rest only further replicates the physiological changes occurring during awakening. Secondly, it has been proposed that the blood sampling procedure employed during the HUT protocol leads to a significant underestimation of haemorheological change. It has been speculated that postural-induced haemoconcentration established in the dependent regions may be poorly reflected in the overall circulation due to uneven or slow intravascular mixing of blood. Lundvall and colleagues found that such an underestimation of plasma volume loss could be avoided if blood was sampled shortly

(<90 seconds) after an individual is returned to a supine position [218]. If this methodological discrepancy has lead to an underestimation of our haemorheological changes, this only adds strengths to the findings that the change in blood viscosity during orthostasis may be clinically significant. Thirdly, a lack of objective measures of hormonal/neurotransmitter activity, capillary pressure, arterial stiffness, and renin/angiotensin II turnover make it difficult to draw definitive conclusions regarding the mechanisms underlying the observed changes during the stress tasks and the hydration manipulation. However, with ethical limitation on blood donation it would have been unfeasible to obtain measures requiring further sampling.

### 4.2.6 Future studies

Although there has been a plethora of research examining the QoL in patients with AF [390], the current study is the first to examine the prevalence of depression and anxiety in patients with AF. Further studies are required to confirm or refute our findings. Future research should also examine the effect of rate and rhythm controlling treatment strategies, as well as the effects of anti-coagulation regimes on psychological and social characteristic. With the follow-up period employed in this study limited to six-months, it would also be of interest to determine whether depression and anxiety have a prognostic value in predicting future cardiovascular morbidity and mortality over a protracted follow-up period.

The current study was also the first to examine the effect of behavioural stress on markers of haemorheology and haemostasis in an AF population. Although future studies examining differences in stress reactivity between different sub-populations of AF patients (e.g. PAF vs. persistent AF vs. permanent AF) may be of interest, insight

may be better served by further investigation of the mechanisms underlying the development of a prothrombotic state during behavioural activities.

The novel finding that enhanced hydration status can significantly lower blood pressure in a hypertensive cohort, in addition to improving endothelial function in patients with AF and hypertension may have considerable clinical implications and should be explored further. Again, investigators would be advised to focus on the mechanisms underlying this response, before determining what type and volume of fluid would provide the optimal improvement in blood pressure and endothelial profile. In addition, it would be of interest to know if the benefits of hyperhydration are confined to patients with hypertension and AF, or whether such a manipulation could be implemented into the care of other patients with established cardiovascular disease.

### 4.2.7 Conclusion

This thesis has demonstrated that (1) AF patients experience a significant degree of psychological morbidity, and (2) mental and postural stress can elicit changes resonant with the development of a prothrombotic state which, in turn, can be attenuated when an individual is hyperhydrated. Such findings provide further insight into level of psychological impairment experienced in this patient population, in addition to further elucidating the potential mechanisms through which behavioural activities can trigger the onset and progression of ACS. The reduction in blood pressure and improvement in endothelial function when hyperhydrated may have potential clinical implications. If these findings are substantiated in future studies, alterations in fluid balance may provide a cheap, side-effect free method for altering an individual's cardiovascular risk profile.

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